NEONATAL HAIR CORTISOL IN RELATION TO MATERNAL ENVIRONMNET, SOCIODEMOGRAPHIC FACTORS, AND INFANT OUTCOMES IN RURAL GAMBIA

by

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Abstract:
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Neonatal hair cortisol in relation to maternal environment, sociodemographic factors, and infant outcomes in rural Gambia
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Maternal stress during pregnancy, whether physical, immunological, or psychosocial, influences maternal physiology and can leave the fetus vulnerable to adverse effects of maternal and environmental stress. The Developmental Origins of Health and Disease hypothesis suggests that the gestational period, through environmental and maternal signals, has significant impact on the health outcomes for the fetus, infant, and later adult. Environmental and maternal signals can be translated to the developing fetus through epigenetic mechanisms, changes in cell cycle regulation and tissue differentiation, and endocrine pathways.

The Gambia is characterized by strong seasonality that, in rural areas, influences maternal workload, food availability, and disease burden. Researchers have linked season of conception and birth to epigenetic modifications, patterns of growth, and adult mortality. While the impact of psychosocial stress on infant health has not been explored in The Gambia, the various forms of stress (e.g. nutritional and environmental) during pregnancy have the potential to affect maternal cortisol and increase the risk of negative birth and infant outcomes.

This thesis explores the influences of seasonality and maternal sociodemographic factors on fetal and infant growth (N=204) in rural Gambia. Hair collected from neonates one week postnatally was processed and analyzed for cortisol. Fetal hair cortisol concentrations (fHCCs) were expected to be higher during the wet season and among low SES mother-infant pairs; significant elevations or depressions in fHCCs were expected to impact growth. Results suggest that fHCCs are not overtly influenced by maternal factors, season of conception or season of birth; however, there were significant associations between male infant growth and fHCCs.

Males with high fHCCs had lower weight, weight-for-height, and mid-upper-arm circumference z-scores at 12 months. A significant association was also found between gestational age and fHCCs such that males with higher fHCCs were born at earlier gestational ages, and female infants with high fHCC were born at later ages compared to low fHCC counterparts. Overall, males seem more sensitive to the effects of elevated fetal hair cortisol than females. These findings suggest that male infants in Gambia may be more immediately vulnerable to intrauterine stress and that there could be lasting consequences on development.

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Introduction

This thesis focuses on the effects of seasonality and sociodemographic factors that shape the maternal environment to explore the relationship external factors may have on birth outcomes, pre- and postnatal growth, and measures of fetal hair cortisol in Gambian infants (N=204). My primary questions are (1) Do fetal hair cortisol concentrations (fHCCs) reflect maternal and environmental inputs? (2) Are prenatal growth measures and fHCCs correlated? And (3) Do fHCCs predict or interact with measures of postnatal growth? Additionally, fHCCs are analyzed in relationship to birth weight and gestational age. Generally, I anticipate that higher fHCCs will be associated with more stressful conditions, either due to seasonality effects or low socioeconomic status (SES). I restrict my use of prenatal growth measures to those taken during the third trimester, where I hypothesize there may be some correlation with fHCCs given the role of fetal cortisol in driving organ maturation and fat deposition in this trimester (Liggins, 1994; Heckmann et al., 2005; Stratakis, 2006; Mustoe et al., 2012). Lastly, I propose a bell curve effect, where low or high fHCCs will have a negative impact on measures of postnatal growth taken ten days after birth, and at three, six, nine, and twelve months. The mechanisms involved in prenatal stress, fetal vulnerability, and associated adverse outcomes are discussed. Followed by a review of studies of hair cortisol and Gambian seasonality. Finally, the theoretical framework of this investigation and project overview are discussed. The primary components and ideas are outlined in **Fig. 1**.

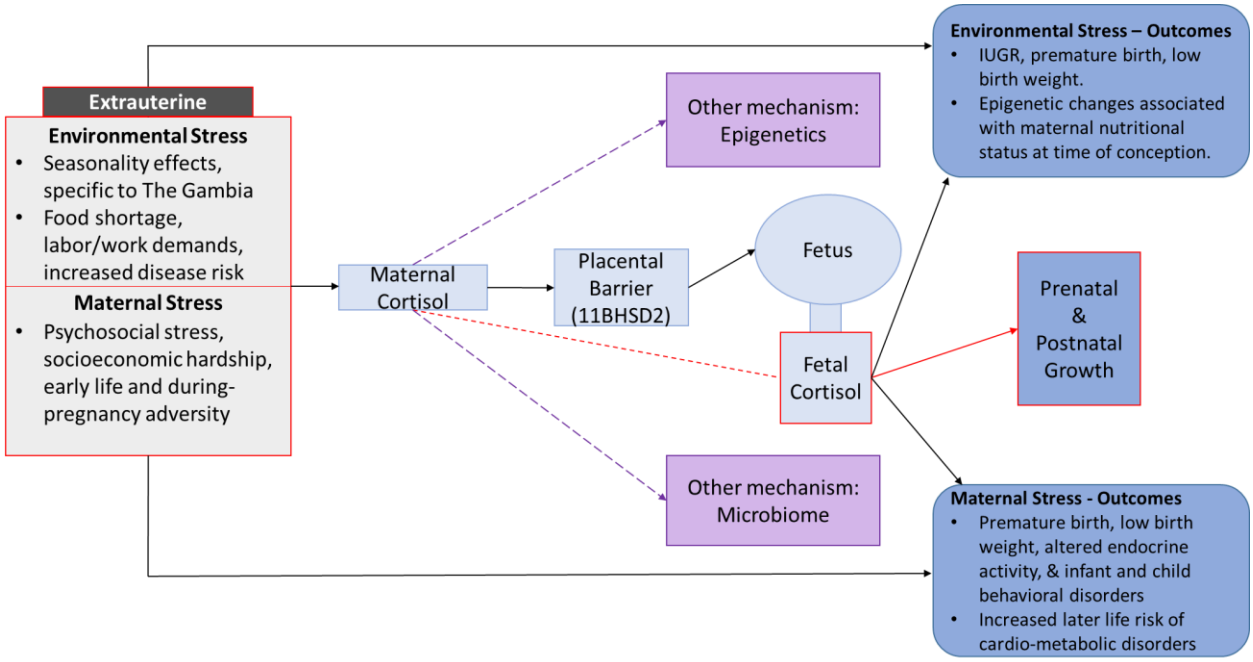

Figure 1 outlines the primary relationships between prenatal stress and infant outcomes. Highlighted is one of the primary mechanisms proposed for how prenatal stress affects the infant: through circulating maternal cortisol and possible placental inefficiency. It is possible the fetus is being directly exposed to maternal cortisol, or that fetal physiology is responding to maternal cortisol with an influx of its own production of the hormone (red dotted line). Other mechanisms (purple) that have been proposed include epigenetic modifications and, recently, the development of the microbiome. Additionally, infant outcomes (blue) associated with environmental stress in The Gambia and others associated with maternal prenatal stress are described. This study will consider if fetal cortisol, perhaps independently of extra-uterine inputs, has any relationship to infant pre- and postnatal growth. Components specifically studied in this thesis are denoted with red outlines/arrows.

i. Maternal Prenatal Stress:

Stress is a notoriously difficult concept to define, despite being widely understood and experienced. For the purposes of this thesis, stress will be defined as the body's response to a challenge, perceived or real. "Stressors" are the challenging stimuli the individual reacts to; in broad categories these can be physical (e.g. nutritional or physical labor), immunological (e.g. infection), or psychosocial, which are often rooted in perception and sociocultural factors. Familial disagreements, desire for/lack of support, and financial pressure are common

psychosocial stressors. Physiologically defined, stress is most often quantified by hypothalamic-pituitary adrenal (HPA) axis function and activity. HPA axis function will be reviewed in a later subsection.

While it has been well documented that maternal stress during pregnancy affects birth outcomes and has long lasting effects on the infant and child (Reviewed by: Baschat, 2004; Van den Bergh et al, 2005; Jansen et al., 2009; Bowers and Yehuda, 2016), the mechanisms by which maternal stress impacts offspring development are poorly understood. There have been two, primary mechanisms proposed for the how maternal stress "transmits" to the fetus: (1) intrauterine environment disruptions to due to variation in uterine artery flow and (2) maternal-fetal hypothalamic pituitary adrenal (HPA) axis dysregulation (Kinsella and Monk, 2009). The first mechanism has not attracted much attention, but the theory behind it is a reported association between measures of high uterine artery resistance and underweight full-term babies and pre-eclampsia in the mother. While one study reported a positive association between artery resistance scores and maternal anxiety, a second was unable to replicate these results (Teixeira et al., 1999; Kent et al., 2002). In addition to hormonal mechanism, the role of epigenetic modifications that influence placental efficiency may be involved in increasing fetal vulnerability to maternal hormones and signals. Additionally, epigenetic changes in the developing fetal brain that may have long-term consequences for HPA axis regulation and function in the infant and later adult which may be involved in some of the outcomes (e.g. behavioral disorders) associated with prenatal stress. The HPA axis and epigenetic mechanisms implicated in prenatal stress and fetal development are described below; a review of the effects of maternal stress during pregnancy follows.

Hypothalamic Pituitary Adrenal (HPA) Axis:

The HPA axis is commonly thought of as the central regulatory system for stress, however this endocrine system and its hormonal end-products (glucocorticoids, including cortisol) are wide acting throughout the body. The HPA axis is essential to maintaining a diurnal pattern of cortisol, which is crucial to healthy sleep/wake cycles, metabolism, growth and reproduction, and immune system function (Chrousos, 2009). Dysregulation of the HPA axis and, consequently, cortisol expression can impact each of these systems. In fact, dysregulation of HPA axis and the diurnal rhythm of cortisol has been associated with numerous conditions, including behavioral and mood disorders, such as major depressive disorder (MDD) (Pariante and Miller, 2001; Pezuk et al., 2012), post-traumatic stress (PTSD) and depersonalization disorders (Heim et al., 2000; Simeon et al., 2001; Ahiara et al., 2007), and cardio-metabolic conditions, such as obesity, insulin resistance and cardiovascular diseases (Penev et al., 1998; Knutsson, 2003; Chrousos and Kino, 2007; Pezuk et al., 2012). The possibility that exposure to maternal stress *in utero* could prime or program an infant's HPA axis and stress response for life has the potential for significant health consequences. This area of research has become a recent tenet of the Developmental Origins of Health and Disease hypothesis (Gillman et al., 2009), and is linked to adaptive responses—either in preparation for the future environment (Gluckman et al., 2005), or as a robust expression of past environments (Wells, 2012). These hypotheses are further explored in "Fetal Programming" below.

Most of the HPA axis' regulatory roles rely on the circadian pattern of cortisol, which peaks in the morning and falls in the evening. The HPA axis, however, remains responsive to stressors at all times. In response to stimulus, the HPA axis initiates a hormonal cascade (**Fig 2a**). The hypothalamus releases cortiocotropin-releasing hormone (CRH), which moves through

the hypothalamo-hypophyseal portal system to the anterior pituitary gland. Here CRH stimulates corticotrophs to produce adrenocorticotropic hormone (ACTH). ACTH enters the bloodstream and acts on ACTH receptors in the adrenal gland, causing the synthesis and subsequent secretions of glucocorticoids (in humans, the primary glucocorticoid is cortisol), into the bloodstream. As a steroid hormone, cortisol acts throughout the body, able to cross the blood-brain and placental barriers, and elicit physiological responses, such as increased blood pressure and heart rate, and down-regulating the production of CRH by binding glucocorticoid receptors in the hypothalamus. This final step provides negative feedback and reduces activity of the HPA axis. It is important to note that cortisol is also involved in gluconeogenesis and immune activity and disruption can have metabolic consequences and lead to immunosuppression (Chrousos, 2009).

During pregnancy, the placenta also produces CRH and can lead to hyperactivation of the HPA axis in healthy women. Studies have reported that the resultant ratio of circulating free or bound cortisol are comparable to those found in individuals with Cushing's disease, an endocrine disorder described by hypercortisolism (Tsigos et al., 2002; Kammerer et al., 2006). This excess cortisol begins during the second trimester and increases linearly with relation to term, with a spike occurring in the last 6-8 weeks of pregnancy (Kammerer et al., 2002 & 2006) (**Fig. 2b**). Biologically, this CRH saturation leads to a blunted cortisol response to acute stress in the mother (Petraglia et al., 2001; Kammerer et al., 2002 & 2006). At 16 weeks gestation, the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts cortisol to cortisone (an inactive form), forms a barrier to maternal glucocorticoids to buffer the thesis (Benediktsson et al., 1997). However, several studies show that in humans 10-20% of maternal cortisol is able to cross through to the developing fetus (Gitau et al., 1998; Glover et al.,

2008). Times of chronic or acute maternal stress, where maternal HPA activity is elevated, may be enough to cause long-term effects on the developing fetus.

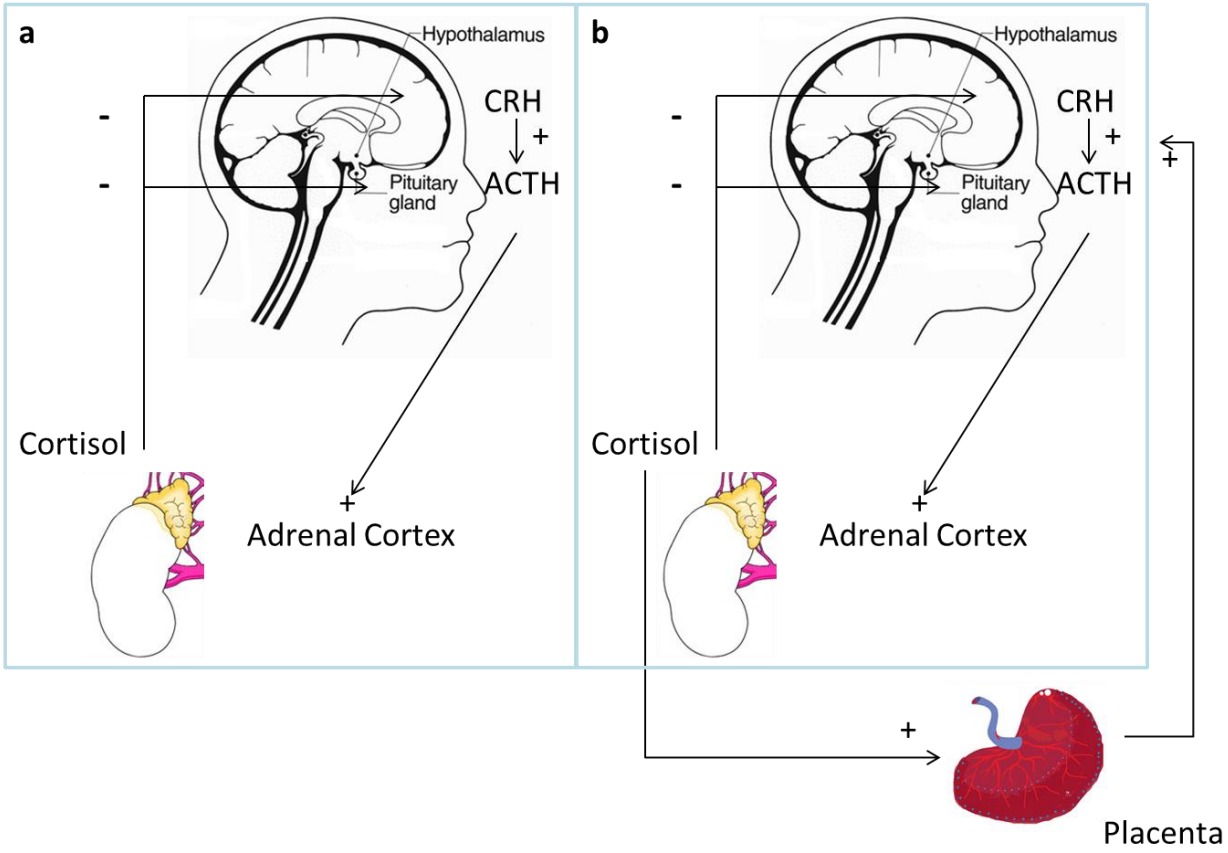

Figure 2: **a.** The hypothalamus releases cortiocotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). In turn, ACTH enters the bloodstream and acts on ACTH receptors of the adrenal gland, causing the synthesis and secretion and release of glucocorticoids, primarily cortisol, into the bloodstream. This steroid hormone acts throughout the body, including on glucocorticoid receptors in the hypothalamus, down regulating CRH activity and consequently providing negative feedback that ultimately reduces activity of the HPA axis. **2b.** During pregnancy, the placenta produces CRH. Here, CRH is shown released from the placenta and upregulating the release of ACTH from the anterior pituitary, stimulating the same endocrine cascade described in part **a**. A primary difference, however, is that cortisol has a positive stimulating effect on the placenta and will encourage the production of CRH, unlike the suppression seen on the hypothalamus leading to hyper activation of the HPA axis.

While it is possible that overexposure to cortisol during pregnancy may have deleterious effects on the fetus and infant, including growth stunting (Rondo et al, 2003; Mustoe et al, 2012),

an appropriate amount of cortisol is necessary for normal functioning of the somatotropic axis, regulating growth hormone secretion, insulin-like growth factor 1, and skeletal bone accumulation, and is involved in nerve and brain development (Spencer et al., 1995; Cianfarani et al., 1998; Renaville et al., 2002; Stratakis, 2006; Wood and Walker, 2016). Hypocortisolism during development may therefore have a negative effect on infant outcome and growth. Both over- and under-expression of cortisol are associated with deleterious effects, including changes in glucocorticoid receptor expression in regulatory centers of the brain and clock gene activity in liver, which would in turn impact metabolic enzyme production and favor obesity risk (reviewed in Wood and Walker, 2016), and the regulatory role of glucocorticoids on bone accumulation could impact growth and later life risk of osteoporosis (Stratakis, 2006).

The third trimester, where placental function may be most vulnerable to elevations in maternal cortisol, is also the time when fetal cortisol production and placental CRH increases. This surge in fetal cortisol drives fetal lung and liver maturation, ensuring the fetus will be capable of breathing independently and meeting thermogenic demands of extra-uterine life (Liggins, 1994). It is also possible that there are ethnic and population differences in baseline HPA axis activity and cortisol levels. Variations in maternal baseline cortisol could impact fetal expression, and without this information it will be difficult to distinguish between abnormality and normal variations; however, few studies have explored this. Those that have were based in the United States and show that African American women do show a different cortisol profile (Glynn et al., 2007; Hajat et al. 2010; Suglia et al., 2010), and some evidence that Hispanic individuals also show a different pattern from white individuals (Hajat et al. 2009). The studies show Black and Hispanic women have generally higher levels of cortisol (Glynn et al., 2007), and lower morning cortisol and slower declines during the day compared to White women (Hajat

et al., 2010)—this pattern of expression is more pronounced in African American women (Suglia et al., 2010). This blunted diurnal rhythm of cortisol has been associated with prenatal stress (Hajat et al., 2010; Suglia et al., 2010; Luecken et al., 2013) and cardio-metabolic and mood disorders (Pezuk et al., 2012). Expanding our understanding of baseline cortisol expression, specifically during pregnancy, and understanding racial/ethnic variation is necessary to understand the range of human variation and important for this field of research.

Epigenetic Factors:

Advancing scientific technology and methodologies have allowed for significant insights into the role of epigenetic modifications that can be transient or long-lasting. A growing body of research has focused on the epigenetic changes involved in fetal programming and suggests that epigenetic modifications are a significant factor in the translation of maternal stress to the fetus, as well as an explanation for the longevity of the impacts reported in offspring. The majority of mechanistic research is limited to animal models, but work in The Gambia (Waterland et al., 2010; Khulan et al., 2012; Dominguez-Salas et al., 2014), on the Dutch Hunger Winter (Lumey and Stein, 1997; Heijmans et al., 2008), the Congo (Rodney and Mulligan, 2014; Kertes et al., 2016), and in Rwanda (Perroud et al., 2014) have shown that maternal environment, nutritional status, and trauma experience at the time of conception and during pregnancy can influence methylation in the infant and have persistent and systemic effects. DNA methylation is a process where methyl groups are added to the DNA molecule, or removed if methylation is 'decreased;' this can change the activity of a DNA segment without requiring changes to the sequence. The results of these epigenetic changes in response to maternal nutritional status, have been implicated in infant immunity and defense mechanisms against infections (Khulan et al., 2012), and decreased methylation at *IGF2* (Heijmans et al., 2008), the gene that codes for insulin like

growth factor II that plays a role in the regulation of growth and metabolism. Together these outcomes have obvious implications for infant growth and mortality by weakening the immune system and stunting growth (Moore et al., 2004; Waterland et al., 2010; Khulan et al., 2012). These studies are discussed in greater detail later in "Fetal Programming."

One suggested mechanism of transmission of maternal stress and cortisol to the fetus is the idea of a threshold, where circulating maternal cortisol elevates past a given point and overwhelms the placental enzymes and reaches the fetus. As a part of this hypothesis, it has been suggested that maternal stress may influence enzymatic activity of 11β-HSD2, which if reduced would impact placental efficiency at converting maternal cortisol to an inactive form, cortisone, before it reaches the fetus (Benediktsson et al., 1997). A study investigating the role of maternal stress during pregnancy and 11β-HSD2 activity in Evans rats showed that prenatal stress was associated with a significant decrease in 11β-HSD2 mRNA and increased DNA methylation at specific CpG site [DNA methylation occurs at the phosphodiester bond (p) between a cytosine (C) and guanine (G)] within the gene promoter in placental tissue (Peña et al., 2012). These changes would cause a significant reduction in the amount of active 11β-HSD2 expressed and, down-regulated, these placental enzymes may no longer be an effective buffer between maternal cortisol and the fetus. The same relationship has been shown in humans, where pregnant women with high scores on anxiety assessments showed down-regulation of 11β-HSD2 (O'Donnell et al., 2012). Additionally, reduced 11β-HSD2 expression was noted in human placenta in association with intrauterine growth restriction (IUGR). Interestingly, this reduction only occurred after the 33rd week of gestation and suggest that impaired feto-maternal glucocorticoid metabolism late in pregnancy increases risk of IUGR and fetal hypoxia risk (Börzsönyi et al., 2011). While Peña et al. (2012) noted a reduction in rat 11β-HSD2 placental expression in

response to chronic restraint stress, within the fetal brain 11β-HSD2 mRNA and DNA methylation were not affected. This may mean that at this point in development, the fetus may be able to buffer against maternal cortisol that crosses the fetal blood brain barrier.

Mueller and Bale (2008) also found possible sex-specific differences in rats, suggesting that male offspring may be at greater risk of experiencing long-term alterations after prenatal stress exposure. Specifically, they found elevated offspring stress reactivity to be associated with increases in gene methylation and activity of both CRH and glucocorticoid receptors (Mueller and Bale, 2008). This means that male offspring of prenatally stressed mothers showed elevated cortisol and exaggerated responses to stressful stimulus when compared to their non-stressed counterparts. Mueller and Bale (2008) noted that early pregnancy stress also caused significant increased expression of the following proteins involved in metabolic processes: PPARα, IGFBP-1, HIF3α, and GLUT4 in male, but not female, placentas. Changes to these specific genes may explain the relationship between prenatal stress and reduced birth weight and the altered growth patterns observed in affected infants, as they would influence insulin sensitivity and metabolic processes.

Changes in expression of placental genes related to growth factors and nutrient support, coupled with the modification to expression of glucocorticoid receptor may have an extensive role in the fetal programming of disease. The glucocorticoid receptor is expressed in virtually all tissue types, including regulatory areas of the brain such as the paraventricular nucleus of the hypothalamus, which is highly stress responsive and responsible for the regulation of metabolism and circadian rhythms (Wood and Walker, 2016). Changes to glucocorticoid receptors have been implicated in many studies of stress and epigenetics (Mueller and Bale, 2008; Perroud et al., 2014; Rodney and Mulligan, 2014; Kertes et al., 2016). In addition, changes to CRH, a known

regulator of serotonin, and a hormonal component involved in stress responsivity could be responsible for the heightened stress sensitivity seen in rodent offspring exposed to prenatal stress (Bale and Vale, 2004; Tan et al., 2004). These collective epigenetic changes may be the primary mechanism by which prenatal stress influences birth weight, cardio-metabolic disorders, and neuroendocrine dysfunction, which increase the risk of psychiatric diseases as seen in adults who were exposed *in utero* to famine during the Dutch Hunger Winter in the second and third trimesters of pregnancy (Susser et al., 1992; Brown et al., 1995).

The sections below review the literature on maternal nutritional and psychosocial stress during pregnancy and related infant outcomes. Due to ethical and technological limitations, invasive studies that are able to explore the epigenetics mechanisms and modifications are often an unrealistic avenue of research. Most studies rely on endocrine measures (e.g. cortisol) or anthropometry.

Intrauterine Stress

a. Nutritional Stress:

While it is possible that nutritional stress has a psychological impact and can elicit a stress response from a mother, nutritional deficiency acts through metabolic mechanisms to impact growth and development. Maternal nutritional status has also been implicated in epigenetic changes that influence insulin sensitivity and glucose metabolism (Jain and Singhal, 2012; Martin et al., 2016). Micronutrient deficiencies have been associated with low birth weight and size, and function of later life metabolism, vasculature, organ growth and function, ultimately leading to an increased risk of cardiometabolic disorders, increased adiposity, and altered kidney function (Baschat, 2004; Cetin et al., 2010; Jiménez-Chillarón et al., 2012; Wu et al., 2012; Gernand et al., 2016). Maternal nutritional stress during pregnancy has been classically

associated with increased risk of heart disease and type 2 diabetes in offspring (Barker and Osmond, 1986; Barker et al., 1989; Barker et al., 1993; Heijmans et al., 2008; Tobi et al., 2009; Cetin et al., 2010; Jain and Singhal, 2012; Jiménez-Chillarón et al., 2012; Martin et al., 2016).

Formation and accumulation of placental and fetal tissue utilizes maternal resources, including energy stores (e.g. glucose, glycogen, and adipose), amino and fatty acids, and relies on maternal diet for essential nutrients (Baschat, 2004; Cetin et al., 2010; Jiménez-Chillarón et al., 2012; Wu et al., 2012; Gernand et al., 2016). Deficiencies in maternal nutrition can quickly lead to placental insufficiency and impact fetal tissue accumulation and, later in pregnancy, growth and fetal physiology (Cetin et al., 2010; Wu et al., 2012; Gernand et al., 2016). 11β-HSD2 has been shown to be sensitive to nutrition, and in rats a low-protein diet was connected with the suppression of 11β-HSD2, meaning the enzyme was unable to convert maternal cortisol to in inactive form before reaching the fetus (Langely-Evans et al., 1996; Betram et al., 2001; Ehruma et al., 2007).

Almost any nutritional deficiency during pregnancy has the potential to have a negative impact on fetal development, birth outcome, or early life growth. Certain nutrients, however, have been implicated specifically for their roles in pregnancy and fetal maturation as crucial. A review of macro- and micronutrients are provided in Appendix A. Many of these are found in nutrient-rich foods, including meat (Cetin et al., 2010; Li et al., 2011; Wu et al., 2012), which are often inaccessible as a regular resource in low-income countries and households who may not have the means to purchase or store it. Micronutrient deficiencies during can result in: preterm birth and IUGR (Castillo-Durán and Weisttaub, 2003; Wu et al., 2012; Ota et al., 2015), low infant birth weight (Ross, 2006; De-Regil et al., 2010; Leffelaar eta l., 2010; Lassi et al., 2013;

McCauley, 2015), and altered brain development and later life risk of mental health disorders (Eyles et al., 2011).

In addition to these outcomes of maternal nutritional deficiency, catch up growth is commonly seen in neonates born at low birth weight. Catch up growth refers to rapid weight, and potentially height, gain in the first months of life. This growth may reduce or erase the initial deficit, but has been associated with later life disease risk (Jain and Singhal, 2012; Jiménez-Chillarón et al., 2012; Martin et al., 2016). Epigenetic modifications that occur in response to nutritional cues have been implicated and may be at the root of many of these programming effects. The stimulus and 'negative' outcome, however, may be the result of an environmental mismatch. Maternal deficiency during pregnancy may not reflect an environment of starvation or inadequate caloric intake but improper nutrition, and can still program the fetus' hypothalamus, altering appetite regulatory genes (Ramamoorthy et al., 2015) or influencing glucose metabolism and insulin sensitivity (Jain and Singhal, 2012; Martin et al., 2016). As a result, the child is at increased risk of developing a metabolic disorder (Jain and Singhal, 2012; Jiménez-Chillarón et al., 2012; Martin et al., 2016). The possibility of nutritional stress in The Gambia is high in rural areas where protein consumption is low and seasonal pressures. Nutrition in the Gambia is discussed further in "Infant Health and Nutrition."

b. Psychosocial Prenatal Stress:

Prenatal psychosocial stress has become a recent focus of study and associated with numerous infant outcomes including preterm birth, low birth weight, heightened stress responsivity, and altered endocrine function (Buitelaar et al., 2003; Davis et al., 2007; Talge et al., 2007; Davis et al., 2012). As inquiry into the role of psychosocial stress and birth outcomes

has expanded, so has the importance of defining stress and understanding what factors lead to a stressful maternal, and consequently uterine, environment (Wadhwa et al., 2011). There are standardized surveys used to quantify stress, some popular ones include Cohen's Perceived Stress Scale (Cohen, 1988), Edinburgh Postnatal Depression Scale (Cox et al., 1987), and the State-Trait Anxiety Inventory (Spielberger et al., 1983). These surveys are commonly used, but other studies rely on interviews, psychological assessments, and biological measures of cortisol without sociocultural or individual context. While it is easy to identify "stress" in communicative participants, it is more difficult to identify the factors that lead to it and allow for maternal mental health to influence fetal and infant health so intensely.

Rooted in the idea of environmental mismatch, meaning signals received *in utero* do not match the lived environment after birth, and fetal programming, having physiological mechanisms that are sensitive to stress during development may prime the infant for a stressful external environment. If an environmental mismatch occurs, though, then the infant, child, and later adult may have a hypo- or hyper-responsive HPA axis. Dysregulation of the HPA axis and the diurnal pattern of cortisol may be impacted, trained, or programmed by early stimuli that occur during fetal development and increase later life risk of numerous physiological and mental illness such as MDD (Pariante and Miller, 2001; Pezuk et al., 2012), PTSD Post-Traumatic Stress (Heim et al., 2000; Simeon et al., 2001; Schider, 2006; Ahiara et al., 2007), and obesity, insulin resistance and cardiovascular conditions (Knutson, 2003; Chrousos and Kino, 2007; Pezuk et al., 2012). Due to the growing realization of the consequences of having a stress response that is improperly tuned to the environment, understanding what enables the adverse health consequences of maternal prenatal stress is crucial. One complex direction researchers are

taking is the role of socioeconomic status and factors on perception of stress during pregnancy and birth outcome.

Socioeconomic status (SES) is most commonly measured as a combination of education, income, and occupation and conceptualized as a social standing or class of an individual or group. Expanding on this latter aspect, SES is often associated with privilege, power, and control, referring to an individual's access to resources and ability to utilize them (American Psychological Association). Most studies exploring prenatal stress effects, with or without the inclusion of socioeconomic factors, have occurred in high-income nations. Near consistently, research shows that women of low SES or who experience significant socioeconomic adversity during pregnancy are at increased risk of prenatal mental health disorders and distress (Fisher et al., 2012), at experiencing stressful life events (Bradley and Whiteside-Mansell, 1997; Ferald and Gunnar, 2009), IUGR (Romo et al., 2009; Kramer et al., 2000), preterm birth and gestational age (Peacock, 1995; Jesse et al., 2003; Larsson et al., 2004; Braveman et al., 2014), and infant behavioral symptoms (Canivet et al., 2005; Hanington et al., 2010; Bouvette-Turcot et al., 2016). These factors and outcomes are summarized in Fardi and Bernstein (2016) and in **Table 1**.

Table 1: A list of factors most often associated with socioeconomic status and the relationship to maternal and infant health.

Socioeconomic Factor		Risk & Consequences
Low education Low income Low class Residence - (environment and crowding) Single Support - (partner, family, community)	Maternal	Increased risk of mental health disorder Increased risk of major life events Greater stress and distress Increased likelihood of poor nutrition
	Infant	IUGR Gestational age and preterm birth Colic Behavioral symptoms

Though most research has been conducted in high-income and western countries, studies based in Pakistan (Rahman et al., 2003; Karmaliani et al., 2007), Bangladesh (Gausia et al., 2009); Ethiopia (Hanlon et al, 2009); and Nigeria (Abiodun et al., 1993; Aderibigbe et al., 1993; Adewuya et al., 2006) consistently report high rates of depression among pregnant and recently post-partum women and commonly cite a desire for social support from their partners and family.

In the Gambia, a qualitative study explored women's experience during pregnancy, childbirth, and the postnatal period (Sawyer et al., 2011). They identified five themes associated with childbearing: a period of transition to adulthood, physical difficulties, children as social currency, children as a source of strain, and the fear of going through childbirth alone, expressing an explicit desire for their husbands to be more involved (Sawyer et al., 2011). For this thesis, I will focus on sociodemographic factors that may contribute to a stressful maternal environment, including education and estimations of wealth, as other SES and measures of adversity are unavailable for this project.

Hair Cortisol:

The free, or unbound to a carrier, fraction of cortisol is incorporated into the hair shaft during growth by diffusing from neighboring capillaries (Cone, 1996; Villain et al., 2003; Anielski, 2008). This portion of the hormone is considered biologically active (Willcox et al., 1985). Studies have shown that steroid hormones [e.g. cortisol (Davenport et al., 2006; Accorsi et al., 2008,), progesterone (Yang et al., 2008), testosterone and estradiol (Liu et al., 1988; Macbeth et al., 2010)] captured in hair are significantly correlated with average concentrations found substrates such as feces (Accorsi et al., 2008), plasma and serum (Gleixner and Meyer, 1997; Yang et al., 2008), and saliva (Davenport et al., 2006). Unlike cortisol measured in feces,

serum, and saliva, which capture short-term expression of cortisol, hair hormone measures provide average concentrations of circulating cortisol over the period of hair growth. Measures determined in hair also have the advantage of requiring only one hair sample to provide an average measure of cortisol expression over a given time (Fourie and Bernstein, 2011).

Hair growth in the fetus begins around 16-20 weeks (Holbrook and Odland, 1978; Gareri and Koren, 2010; Montagna and Ellis, 2013), although variation in the initiation and rate of hair growth in utero is largely unknown (Holbrook and Odland, 1978); therefore, hair collected during the first week of life can potentially capture fetal hair expression from about half of the second trimester through the first week of life. Hair has been used to explore cortisol expression of macaque (Kapoor et al, 2014 and 2016; Grant et al., 2016) and human neonates (Yamada et al., 2007; Hoffman et al., 2016). However, only one of the human studies (Hoffman et al., 2016) collected the samples within one week of birth and reported their findings with respect to prenatal stress. Interestingly, they found no correlation between maternal perception of stress, or other factors related to maternal stress including: sociodemographic factors, parity, mode of delivery, infant sex, race/ethnicity, or tobacco use and fetal hair cortisol concentrations (Hoffman et al., 2016). The reported values of neonate hair cortisol are summarized in **Table 2** below.

Table 2: Summarizes results from the only studies that report values of neonatal hair cortisol in humans and nonhuman primates.

Study	Species	Neonate age at collection	Hair cortisol mean (pg/mg)	Context
Yamada et al. 2007	Human	30 days	805 ± 760	Infants with an extended stay in the NICU (N=60)
Hoffman et al. 2016	Human	0 days (birth)	281.8 ± 141.6	Denver population of women participating in a study of prenatal stress effects (N=90)
Kapoor et al. 2016	*Macaca mulatta*	2 – 4 days	820 ± 300 (stressed)	Stress effect on neonate hair cortisol (N=22)

			1040 ± 300 (control)	
Grant et al. 2016	*Macaca nemestrina*	0 days (birth)	1027 ± 97.9	N=13

Hoffman et al. (2016b) showed a significant correlation between higher perceived stress and maternal hair cortisol. They did not find a significant relationship between maternal hair cortisol concentrations or maternal sociodemographic data and fetal hair cortisol expression (Hoffman et al., 2016a). Maternal hair cortisol during gestation, however, does follow the expected biological pattern, rising through the trimesters and peaking in the third trimester (Sandman et al., 2006; Glynn et al., 2007; Kirschbaum et al., 2009; D'Anna-Hernandez et al., 2011; Hoffman et al., 2016b). In *M. nemestrina* the rise in maternal hair cortisol during pregnancy was significantly correlated with newborn hair cortisol (r=0.55), such that a greater increase in maternal cortisol during gestation was related to newborn hair cortisol (Grant et al., 2016), suggesting that fetuses were exposed and sensitive to maternal cortisol expression and experience of stress *in utero*. Macaques begin growing hair approximately 28 days gestation, two months before term (Kapoor et al., 2014). While primate models are often favored in biomedical research for their similarity to humans, it is important to note the difference in rate of development. Macaques are born precocial, while human infants are secondarily altricial—this difference in neurological development may impact the activity of the HPA axis and cortisol expression in utero and early life.

ii. Fetal Programming:

Fetal programming is founded on the idea that a stimulus or insult to the fetus, or one that impacts the intrauterine environment, during a critical point of early life affects the structure, physiology, and metabolism of the fetus or infant with lasting consequences for the adult

(Godfrey and Barker, 2001). Consequences of negative intrauterine experiences have been associated with cardio-metabolic disorders such as coronary heart disease and obesity (Barker et al., 1993; Frankel et al., 1996; Stein et al., 1996; Rich-Edwards et al., 1997; Barker, 1998; Godfrey and Barker, 2001). Fetal programming may result from adaptive, compensatory mechanisms that occur when the maternal-placental nutrient supply fails to meet fetal demand (Barker et al., 1993; Godfrey and Barker, 2001; Gillman et al., 2007; Uller, 2008; Badyaev and Uller, 2009; Wadhwa et al., 2009). If the fetus is nutrient deprived, meaning the supply from the mother and placenta is inadequate, epigenetic and endocrine modifications may be advantageous for survival by reducing energy demand (e.g. growth retardation) and/or favoring opportunistic mechanisms (e.g. insulin resistance).

The idea of "fetal programming" developed from the Fetal Origins Hypothesis, which was primarily based on David Barker's work on the consequences of nutritional stress during pregnancy (as indexed by birth weight) and the relationship to adult incidence of ischemic heart disease (Barker and Osmond, 1986; Barker et al., 1989; Barker et al., 1993). The theory was developed across three primary papers (Barker and Osmond, 1986; Barker et al., 1989; Barker et al., 1993). In the final one, Barker et al. found that nutritional stress during early pregnancy, due to hyper- or hypoglycemia, and maternal diabetes was associated with reduced birth weight and infant growth stunting. They proposed that "undernutrition during gestation reprograms the relationship between glucose and insulin [and consequently] between growth hormone and IGF [insulin-like growth factor]" (Barker et al., 1993, p. 940). This would mean that a maternal signal could cause permanent changes in the body's structure, function, and metabolism, impacting fetal and infant growth and development. This became the basis of the "fetal origins hypothesis," and motivated significant interest and research into developmental plasticity and the effects of

intrauterine experiences. Research over the next decade remained focused on the impacts of maternal nutrition on birth outcome and later life health, the emphasis being on explaining obesity, metabolic and cardiac disorders (Wadhwa et al., 2009). In the next decade, research expanded with the transition to the Developmental Origins of Health and Disease (DOHaD) hypothesis, which now focuses on a broad scope of developmental cues that influence the developing gametes to the infant and adulthood (Gillman et al., 2007). Specifically the aims of DOHaD have extended from (1) developing the theory of predictive adaptive responses of the fetus to the environment and the consequences of mismatch and the origins of obesity. and (2) under/over nutrition during pregnancy to now evaluating the (3) psychobiological effects of stress during pregnancy and (4) investigating the roles of epigenetic changes as a mechanism that causes, or translates, maternal and environmental cues to the fetus, and as an explanation for the long-lasting effects of the intrauterine environment and resultant disease risk in later life (Gillman et al., 2007; Wadhwa et al., 2009).

One of the central aims of DOHaD is to develop a theory based on the relationship of predictive adaptive responses (PAR) of fetus to diverse environmental cues and the consequences of mismatched prenatal and postnatal environments (Gluckman et al., 2005; Gillman et al., 2009). Gluckman's (2005) PAR hypothesis suggests that the mechanisms influence the intrauterine environment and fetal development are oriented toward predicting future environments. This, however, has been critiqued (Rickard and Lummaa, 2007; Bogin et al., 2007; Wells, 2007 & 2012) because in many ways it assumes that an adult human environment will be predictable. There is little historical and evolutionary support for such as a claim, rather the opposite (Potts, 1998). Additionally, many traits that are associated with later life adult disease are strongly associated with early life survival, indicating a trade-off (Bogin et

al., 2007; Wells, 2012), which is particularly crucial for humans and other apes as mortality in human foraging populations is greatest in the first few years of life (Wells, 2000). Ultimately, Wells (2012) argues in contrast to the PAR hypothesis, that these responses are more likely reflective of the past, where the traits that improve infant survival are still expressed, despite later-life, adult consequences.

Underlying both arguments are mismatched environments (**Fig. 4**), that is that signals during gestation are priming the infant for an environment that differs from the lived, postnatal one. It is also an example of how it can be misleading to conceptualize modern standards of health and longevity without grounding our understanding in evolutionary theory, where trade off and infant survival and successfully reaching reproductive age are likely deeply engrained in adaptive mechanisms and responses. Although I focus on proximate mechanisms, this project is framed by evolutionary theory and findings may have broader implications. Prenatal stress research is traditionally clinical, meaning it may function within a narrower scope that does not emphasize the importance of human variation, adaptive mechanisms, and the evolutionary pressures that have been and may remain responsive to stimuli/environments.

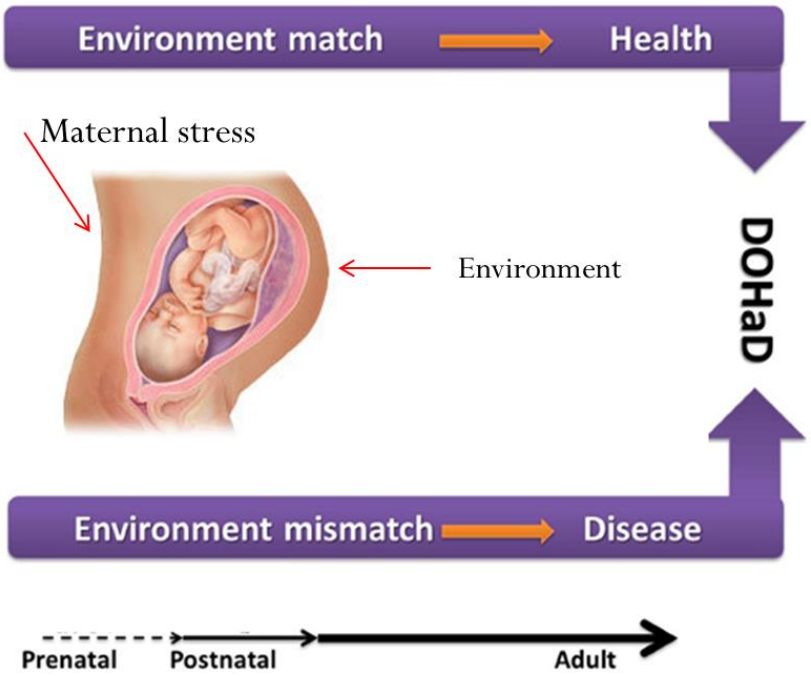

Figure 3: The Developmental Origins of Health and Disease hinges on the concept of environmental mismatch. Maternal and environmental cues create the intrauterine environment; some stimuli can cause long-lasting, permanent changes in fetal physiology. These changes prime the infant for the perceived external environment. If these stimuli are accurate or if the environment is stable, then the outcomes for the infant are largely healthy. When a postnatal environmental mismatch occurs, the risk of developing diseases in adulthood increase.

Epigenetic and endocrine systems are thought to be strongly involved in these adaptive responses and implicated in the long-term health consequences described in adults. Both systems are sensitive and malleable during early developmental periods. These mechanisms enable a range of physiological plasticity without requiring permanent changes to the genome. These phenotypic changes would prime the offspring for the postnatal environment, ideally improving fitness, while allowing for the preservation of genetic diversity, while negative outcomes occur due to a mismatch between what the intrauterine environment suggests and the later-lived environment of the offspring (Gluckman and Hanson, 2004). These mismatches can be due to rapid changes in the environment, which in a highly seasonal environment may prepare an infant to cope with a differentially challenging environment with differentially available resources.

However, in lieu of the PAR hypothesis, it is possible that the adverse outcomes seen in response to stress, such as reduced body weight (Mulligan et al., 2012), catch up growth Martin et al., 2016), and altered endocrine function (Gutteling et al., 2005), may have advantages by reducing energetic cost during critical time periods and taking advantage of resource rich periods. In such a case, the preparation and normal response might be to prepare for that of a harsh environment, and when it does not occur the consequences can be more immediately deleterious, manifesting as altered cognition or behavioral disorders (Buitelaar et al., 2003; Davis et al., 2007; Talge et al., 2007; Davis and Sandman, 2012), with worsening consequences in adulthood such as cardio-metabolic diseases (Baschat, 2004; Cetin et al., 2010; Jiménez-Chillarón et al., 2012; Wu et al., 2012; Gernand et al., 2016).

While many of these changes to epigenetic and/or endocrine pathways occur within the life of a single individual, there is evidence of intergenerational effects. Individuals exposed to famine during late pregnancy have been described as giving birth to small-for-gestational age babies (Lumey and Stein, 1997); these second-generation females did not bear children that followed the pattern of increasing birth weight with birth order, which suggests an altered physiology, and predicts that third-generation offspring will also be born small (Lumey and Stein, 1997*).* Similarly, African American women are at increased risk to deliver premature infants (Hargraves et al., 2003), and a recent study showed that even with upward social mobility and improved living situation and health care access the risk for premature birth remained consistent (Collins et al., 2011). This implies that there may be epigenetic mechanisms driving these outcomes.

Additionally, Lumey and Stein's (1997) work on the Dutch Hunger Winter shows some of the consequences of aberrant, abrupt stressful changes while studies of war-torn regions.

Studies of pregnant women in the Democratic Republic of Congo (Rodney and Mulligan, 2014; Kertes et al., 2016) and the Tutsi in Rwanda (Perroud et al., 2014), show significant genome-wide epigenetic changes that can be identified in both the mother and infant in response to extreme war-related stress. These studies suggest that in women who have experienced repeated traumas have epigenetic modifications that can be transmitted to their children.

iii. The Gambia

Overview:

The Gambia is a small country, with a population of 1.9 million people (UNICEF, 2015), located on the West Coast of Africa, surrounded by Senegal (**Fig. 3**). It gained independence from the UK in 1965. Rural Gambians mostly live an agro-pastoralist lifestyle, relying on agricultural and animal gains, whether directly or through monetary returns from market sales. There are five major ethnic groups in the country: Fula, Jola, Serahule, Wolof, and Mandinka, with the latter being the largest single ethnic group in The Gambia. Individuals recruited to this study live in the Lower River Region, including the village of Keneba where the clinical and research buildings are located, and sixteen surrounding villages.

The World Health Organization (2013) reports childhood mortality 4.9% for infants under 1 year and 7.29% for children under 5. With medical intervention and clinic support, infant and childhood mortality rates are decreasing, however, this rate of mortality constitutes an unacceptable amount of loss. Totaling neonatal, infant, and under five deaths 11,018 children died in 2012, out of 77,229 births, that is a 14% death/birth rate. This rate has greatly improved in recent years, but remains a devastating rate of loss compared to the US where infant mortality is 0.006% (UNICEF, 2015). This, coupled with the pressure and importance for women to conceive, has the potential to create a stressful environment (Bledsoe, 1994; Bledsoe et al., 1998;

Sear et al., 2002; Hough, 2010). The sociocultural context and pressures on women discussed in the next section informed my decision to include sociodemographic factors as potential stressors.

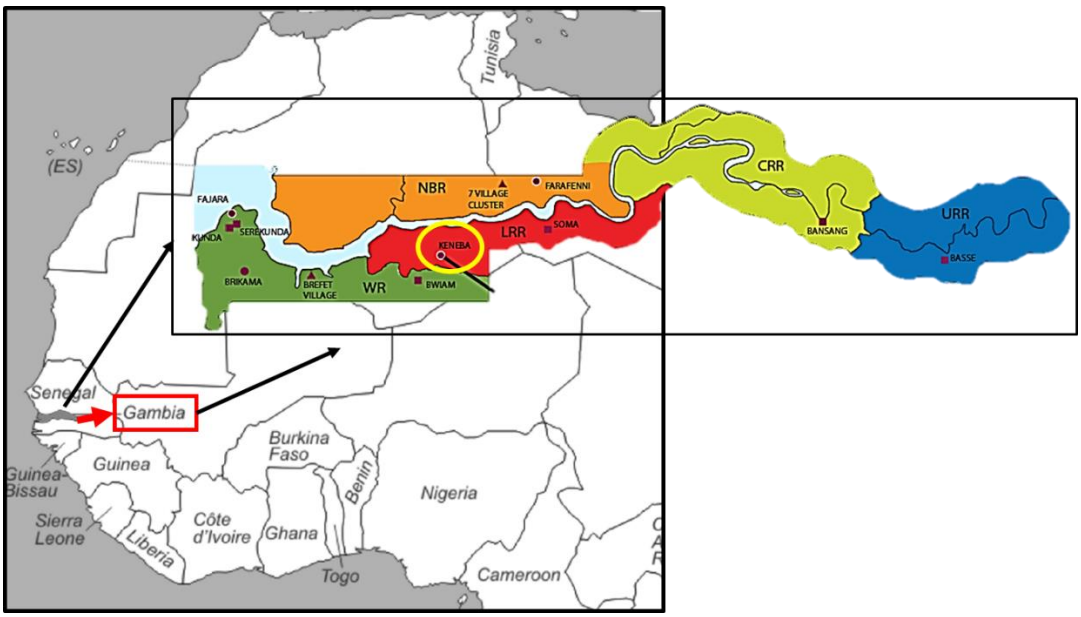

Figure 4: A map of West Africa and Gambia. Gambia is boxed in red on the large map. On the zoomed map, the Lower River Region is red and Keneba is circled in yellow.

Sociocultural Context:

Among the Mandinka, polygyny is a widespread cultural practice, reinforced by Islam, the Gambian state, and traditional customs (Wittrup, 1990). The practice may be rooted in the belief that there is a surplus of women and if a man can maintain equality among them, a man may have up four wives (Wittrup, 1990). Several studies have taken an economic approach to understanding polygyny and the benefits, exploring if household efficiency (Dauphin, 2013) or if rates of cooperation and altruism increase (Akresh et al., 2011a, 2011b). However, findings suggest that 'benefits' are largely based on broader sociocultural dynamics or individual relationships within the household. Fewer studies have considered the way health can be impacted by these complex social relationships. Health studies have largely focused on

transmission of sexually transmitted diseases and the potential vulnerability to illness (Bove and Valeggia, 2009).

Poor communication between spouses and potential age and power imbalances can have an isolating effect on wives and create competition between them (Wittrup, 1990; Bove and Valeggia, 2009). Wittrup (1990) wrote a detailed, qualitative report of her time among the Mandinka and describes highly individual-based reactions towards the prospect of a new wife. She gives evidence of women who want cowives because they will be better able to manipulate power within the household and even sway the choice in wife; on the other hand, she describes a desire for cowives to increase support for each other, ultimately increasing autonomy and freedom of mobility (Wittrup, 1990). Even in the more altruistic and supportive instances of polygynous relationships, intense jealousy underlies each shared experience resulting in a "gnawing uncertainty within each and every woman, as a time bomb that can explode at any time" (Wittrup, 1990, p. 130).

Beyond the poetic prose, is the potential for very real stressors. Navigating these social complexities and the desire for support during pregnancy, a potential period of vulnerability, could be a source of emotional distress. In fact, polygamy has been associated with higher levels of anxiety and depression in women in The Gambia (Bove and Valeggia, 2009) [additionally, it has been associated with increased rates of depression in Nigerian women (Adewuya et al., 2007)]. The desire for support and autonomy are directly cited in interview-based studies of the maternal experience in Gambia and suggest that the absence of this kind of support may be a point of stress (Bove and Valeggia, 2009; Sawyer et al., 2011).

Seasonality and Health:

"Rains bring the hungry season" (Prentice and Prentice, 1988). The wet season in the Gambia begins in summer months, stretching from late June to October. This period is characterized by increased humidity and rains, which causes an increased risk of malaria and parasite infection, an increased and intensive agricultural workload for women, and is accompanied by food shortage (Prentice and Prentice, 1988; Moore et al. 1997; Anya, 2004). The Gambia relies primarily on subsistence agriculture and their productivity consists of various cereals, namely rice crops and maize, and ground nuts (Webb, 1989). On average, women supply 30% of the labor (Webb, 1989; Ulijaszek, 1993; SOFA team and Doss, 2011). This is variable in different parts of Gambia, for different ethnic groups, and in upland and lowland Gambia. For traditional rice crops, women can supply over 70% of the labor force (Webb, 1989).

A woman's workload will lessen during the course of her pregnancy until the month before delivery when she works 25% less than that of non-pregnant women (Roberts et al., 1982). However, depending on the season of her pregnancy this can still involve a heavy work load. Based on data of women working in rice fields, pregnant women transition from 50% time of a 15 hour work day in the dry season to 83% in the wet (Roberts et al., 1982). Seasonal labor demands and changes for pregnant and lactating women are described in **Table 3**. Additionally, these increased labor demands coincide with a general food shortage. The end of the dry season and onset of the wet requires utilizing depleting resources from the previous harvest.

Woman's Status	**Dry Season (hours/day) (% time)**	**Wet Season (hours/day) (% time)**
Not reproductively active	15 hours (100%)	15 hours (100%)
Lactating	8.25 hours (55%)	13.8 hours (92%)
Pregnant	7.5 hours (50%)	12.45 hours (83%)

Table 3: Shows the changes in labor over the year for women of different reproductive status, based on data from Roberts et al., 1982. Percent time is based on a 15-hour work day.

Due to the increased rains, and consequent increase in stagnant water, the risk of malarial infection increases significantly from June to October. The River Gambia and its tributaries provide breeding grounds for malarial parasites (Jawara et al., 2008). Clinical cases of and mortality due to malaria peak between September and November before rapidly declining (Greenwood et al., 1987). The wet environment proves favorable environment for other parasites as well and incidences of diarrhea, while common and potentially persistent throughout the year, increase significantly during this season. These outbreaks of gastroenteritis can have severe, adverse effects on infant growth (Cole and Parkin, 1977; Rowland and McCollum, 1977; Eccles et al., 1989; Jaffar et al., 1997; Poskitt et al., 1999; Lunn, 2000).

Food shortages and increased disease cause seasonal weight loss in adults and can have the potential impact to fetal growth (Prentice et al., 1981; Moore et al., 1997; Rayco-Solon et al., 2005; Olowabi et al., 2015). These impairments on the fetus and impacted infant can be long lasting and result in growth faltering events, where a child "falls off" their growth curve during infancy. In urban and some rural areas, these children can 'catch up' with their growth curve if given necessary supplements and nutrition, but if the malnutrition is extreme during the wet season, they may not be able to reach their genetic potential (Tomkins et al., 1986). It has been shown that infection and gastroenteritis have roles in the severity of growth stunting as it can exaggerate nutritional deficiencies; even as rates of gastroenteritis have improved, infant mortality due to malarial and acute respiratory infections have been historically high (Jaffar et al., 1997) and growth remains impacted (Eccles et al., 1989; Poskitt et al., 1999; Lunn, 2000).

To imply that these effects even in the best of situations are temporary, however, leads to an oversimplification of the consequences of malnutrition and early life experiences. Research

has shown that season of birth can predict mortality in rural Gambia, such that people born in the "hungry season" are up to ten times more likely to die during young adulthood and later life (Moore et al., 1997; Collinson et al., 2003). Season at the time of conception has been linked to epigenetic modifications to genes associated with infection and immune response (Waterland et al., 2010; Khulan et al., 2012; Dominguez-Salas et al., 2014). Seasonality effects, whether during periconception or during gestation, suggest programming of the fetal immune system. Evidence of fetal programming (Moore et al., 1997; Collinson et al., 2003; Waterland et al., 2010; Khulan et al., 2012; Dominguez-Salas et al., 2014; Moore, 2016) and intergenerational effects, where season of maternal birth was linked to offspring birth weight and head circumference size (Rickard et al., 2012), implies significant pressure on developmental systems during critical periods of growth and suggests that small size may be an adaptive mechanism to reduce energy demand by slowing growth rate.

A study comparing Gambian conditions to a population in Bangladesh found that while there was a similarly high infant mortality rate within the first year of life for those born during the hungry versus the dry season in Bangladesh, this effect on mortality could not be extended to premature deaths during adolescence (Moore et al., 2003). This suggests that the fetal programming effect being described in the Gambia may be the result of chronic, intergenerational stress, and/or the result of interactions between nutritional, immunological, and psychosocial stressors on the mother.

Infant Health and Nutrition:

Maternal health can directly influence fetal development and health. There is a documented effect of seasonality on birth weight, specifically a significant reduction is seen

during the wet season in The Gambia (Roberts et al., 1982; Moore et al., 1997; Rayco-Solon et al., 2005). Incidences of overall small infants are high in the Gambia; out of ~2000 births, half were small in some way: 13.3% of births were low birth weight, 12.3% were born premature, and 25.1% born small-for-gestational age (Rayco-Solon et al., 2005). Incidence of premature births (<37 weeks gestation) follow the pattern of agricultural labor, peaking in July along with labor demands, and again in October when incidence of malaria infection rises. Prevalence of infants born small-for-gestational age were highest at the end of the wet season (Rayco-Solon et al., 2005; Fulford et al., 2006), and likely a direct effect of poor maternal nutrition and infection during late pregnancy.

To evaluate the efficacy of the many intervention and supplementation programs in Gambia, Owolabi et al. (2015) examined patterns of birth weight over a four-year period to see if there were improvements. They found that, while there was a seasonal variation, there was also an overall decline in birth weights; 5% of all births during the study period were low birth weight, even in urban environments. They propose that environmental and climatic changes, possibly with global economic down turn have led to a decline in the quality of maternal nutrition, and to poor antenatal care.

Seasonal weight loss is as common among children as it is adults (Prentice et al., 1981; Moore et al., 1997; Rayco-Solon et al., 2005; Olowabi et al., 2015). For infants, these periods of low resources can prevent weight gain and lead to growth faltering and long term stunting.

In rural areas, it was initially assumed that the reduction in weight and growth rate in children was due to malnutrition, however because the effect was also seen in urban communities where there was no shortage of food (Tomkins et al, 1986; Olowabi et al., 2015), immunological stress and infections may be driving the weight loss and poor growth rates.

Malaria is a likely contributing factor, but researchers argue that gastroenteritis may cause more morbidities as medications for malaria are readily available (Cole and Parkin, 1977; Tomkins et al., 1986; Campbell et al., 2003). Gastroenteritis is most often caused by a viral infection and is a primary cause of diarrhea. Risk of infection and incidence of diarrhea are highest during the wet season, most likely due to poor food and water hygiene along with environmental conditions that allow for stagnant water.

Infection also creates a cycle of undernutrition. Diarrhea causes significant loss of consumed nutrients and viral infection can also lead to depressed appetite. For infants and toddlers who are breastfeeding, which is common until two years of age, a loss of appetite can cause a decline in milk production and lessen their nutritional resources (Prentice and Prentice, 1988). The ability to recover is where the growth patterns of urban and rural children diverge. While seasonal growth stunting has been described in both communities, in rural areas the combination of infection and malnutrition can result in permanently depressed childhood growth where it seems the ability to recover and catch up to growth curves is greater in urban communities (Tomkins et al., 1986). This may be due to fetal programming that results from early exposure to these stressors, or chronic and repeated exposures to nutritional and immunological stressors in rural areas, where they may be more aberrant in the urban population.

There have been numerous supplementation programs to try and improve these conditions, nutritional deficiencies, and outcomes. In rural Gambia, refrigeration is uncommon in rural areas given a widespread lack of access to electricity and consequently it is unlikely that women have regular access to high protein dense foods. In fact, villagers depend mostly on cereals and groundnuts, which are subject to seasonal variation, and consume generally low protein (McGregor and Smith, 1952; Prentice et al., 1993; Prentice and Paul, 2000; Thurnham et

al., 2011). In the dry season, there is a significant increase in energy demands combined with reduced resources that have the create a harsh nutritional environment. The results of these periods of seasonal stress have been described in association with increased infection, small-for-gestational age and low birth weights, IUGR (Roberts et al., 1982; Prentice and Prentice, 1988; Rayco-Solon et al., 2005; Owolabi et al., 2015), and possible altered immune function (Tomkins et al., 1986; Moore et al., 1997; Moore et al., 2003; Anya, 2004).

Rural Gambia has a history of a supplementation programs to alleviate deficiencies like a low iron and riboflavin (B2) status (Bates et al., 1982; Powers et al., 1983; Wegmüller et al., 2016; Prentice et al., 2017), a low calcium diet (Dibba et al., 2000; Jarjou et al., 2006, 2010; Hawkesworth et al., 2011), periodic availability of vitamin A (Thurnham et al., 2000), and the benefits of lipid-based supplements are being investigated (Moore et al., 2012; Johnson et al., 2016) on pregnant women and/or children. Calcium supplementation programs have proved harmful, rather than beneficial, where researchers suggest this is because the sudden addition of calcium to the diet disrupts metabolic adaptations that have been made to accommodate its absence (Jarjou et al., 2006&2010; Hawkesworth et al., 2011). Zinc deficiency has also been considered, but found to be an ineffective supplement to improve growth in Gambian infants and children, except for a few notably vulnerable positions (Bates et al., 1993). The lipid-based supplements being investigated as part of the Early Nutrition and Immune Development project (Moore et al., 2012) do not appear to provide a growth advantage (Johnson et al., 2016). All of these deficiencies have the potential to cause nutritional stress, potentially interact with placental efficiency, especially due to the low-protein intake of Gambian women and have deleterious effects on fetal and infant growth (Ceesay, 1997; Prentice et al., 1993; Prentice and Paul, 2000).

It is important to note that low iron status is common in Gambian children (Powers et al., 1983; Prentice et al., 2017) and that anemia can increase disease risk. Good sources of vitamin A are also only periodically available during mango season (Thurnham et al., 2000); if maternal vitamin A deficiency occurs during gestation, the fetus may experience nutritional stress and contribute to immunological deficiency during infancy (Thurnham et al., 2000; Ross, 2006; McCauley, 2015). In addition to the low and potentially inadequate nutrients, it is also a common and widespread practice to introduce weaning foods at ~four months, two months before the World Health Organization recommends (Eriksen et al. 2016). This can put increased nutritional stress on the infant, impact growth, and increase risk of immunological complications and has been associated with the high rates of gastroenteritis in infants in Gambia (Barnell and Rowland, 1979; Prentice, 1993; Poskitt et al., 1999; Thurnham et al., 2000).

iv. Project Overview:

I explore the relationships between the maternal environment, measured through seasonality and sociodemographic factors on fetal hair cortisol expression. Additionally, the interactions between these environmental and maternal factors, and fetal hair cortisol, will be considered to determine if they are strong predictors of prenatal growth, birth outcome, and infant growth from birth until one year of age (**Fig. 5**). This thesis will make a needed contribution to the investigation on how maternal stress translates to the fetus, and explore the usefulness of fetal hair cortisol in describing fetal exposure to prenatal stress and a predictor of infant health and success.

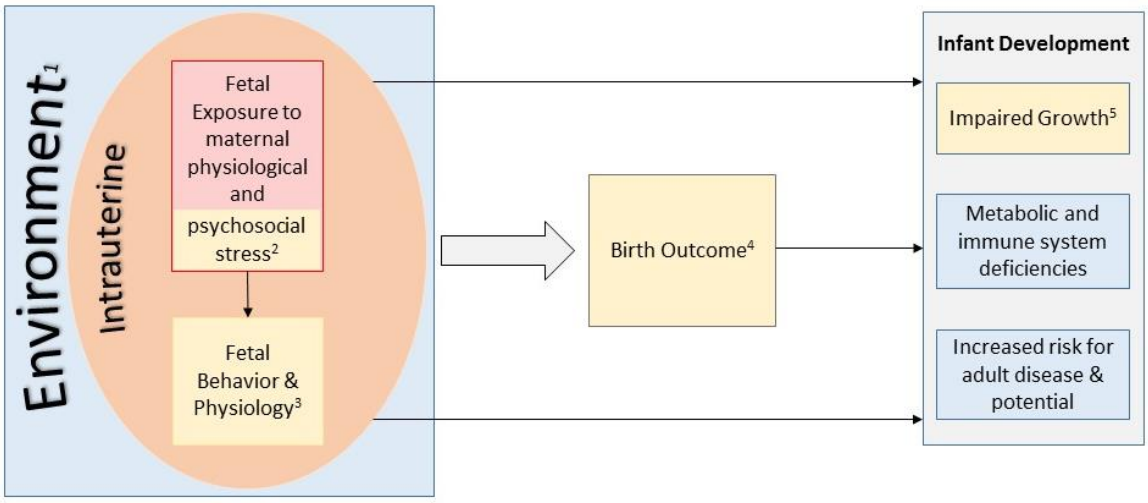

Figure 5: Outlines prenatal stress effects on fetal behavior which can lead to altered birth outcome and ultimately impaired infant growth and health. Measures included in this thesis are highlighted in yellow boxes and described below:

1. Season of conception and season of birth
2. Maternal sociodemographic factors as proxy measures of stress

3a. Third trimester prenatal growth measures

3b. Fetal hair cortisol

4. Gestational age and birth weight
5. Infant growth from birth until 12 months of age

Pregnant women were recruited into the Hormonal and Epigenetic Regulators of Growth (HERO-G) project (Principal Investigator: Dr. Robin Bernstein). The HERO-G project has a concentrated focus on understanding the physiological mechanisms involved in growth faltering in rural Gambian infants. These mechanisms are responsive to nutrition, environment, and infection—forms of physiological stress. In this thesis, I utilize maternal sociodemographic data and measures of pre- and postnatal growth from the larger HERO-G study. Women were recruited from seventeen villages in the West Kiang Region of The Gambia. The hair samples (N=204) analyzed in this thesis were collected at the naming ceremony, seven days after birth where it is customary to shave the infant's head. Field work and sample collections were

performed by a field team, while I completed all sample processing, wet lab analysis, and data analysis.

Methods

Prenatal:

Women of reproductive age, 18-45 years old, living in the West Kiang region of Gambia were invited to participate in the study. Of those who enrolled, I use information from women living in 17 rural villages. A total of 206 hair samples were collected by field assistants from infants in their assigned villages, however two were left out due to insufficient sample weight (N=204). Prior to conception, women were visited monthly by field workers and began clinic visits one week after a positive pregnancy test. At these clinic visits, in addition to a full antenatal checkup, sociodemographic data and life history information was collected (e.g. parity, years of education, livestock ownership). Data was anonymized to protect participant information. Available maternal factors are described in **Table M1**, however, not all factors were used due to large amounts of missing data (e.g. maternal weight).

Table M 1: This table lists the possible maternal factors based on available data, along with notes on how some factors were calculated and why others were not used.

Maternal Factor	**Notes**
Maternal Education	
Years of School Arabic	Total years of schooling in Arabic
Years of School English	Total years of schooling in English
Total Years Education	Combined years of education in English and Arabic
Children Alive	Number of children a woman currently has
Children Dead	Children "dead," "stillborn," and "miscarried" were provided as options to self-describe the loss of a child (collected as a numerical value)
Children Stillborn	
Children Miscarried	
Lost A Child category	If a child was lost, through death, stillbirth, or miscarried: Y/N
Parity	
Parity	Number of children delivered
Parity category	Primparous or Multiparous
SES Factors	
# of rooms	Number of rooms within a household
# of people living in rooms	Number of household occupants

Crowding Ratio	Crowding ratio = Number of rooms/Number of people
# of Sheep	Number of livestock belonging to mother's household
# of Cows	
# of Goats	
Cart	If the mother's household possesses a cart
Total Animals	Total number of livestock in mother's household
Proxy Wealth	Calculated by assigning weighted values to livestock type and cart, and summing values.
SES Score	Summation of livestock, cart, education, and family size. See text for details on calculation.
SES category	Determined based on distribution of SES score
Maternal Physiological Factors	
Maternal Age	Colinear with Parity; Parity used in analysis
Maternal Height	

At these clinic visits, fetal growth measurements were also taken via ultrasound. They were used to estimate fetal age and determine the timing of follow up visits. For example, if a fetus' estimated age was between 20 and 28 weeks, follow up visits and fetal measures were taken again at 28 and 36 weeks gestation. However, women who were already pregnant up to 28 weeks were still recruited into the study, meaning fetal growth data and maternal weight measurements are not available across the full duration of a pregnancy for all participants. The prenatal growth measures that were taken are defined in **Table M2**.

Table M 2: Lists the different prenatal growth measures taken, their abbreviations, and the frequency of the measurements.

Prenatal Growth Measure	**Acronym**	**Frequency of Measure**
Crown Rump Length	CR	Measurements taken at <20, 20, 28, 36 weeks, when possible
Abdominal Circumference	AC	
Head Circumference	HC	
Occipitofrontal Diameter	OFD	
Femur Length	FL	
Tibia Length	TL	

Postnatal Growth:

Field assistants attempted to attend all deliveries to collect samples and record birth weights. Birth months and villages were also used as environmental factors; distributions of participants are described in **Tables M3 & 4**. Following the naming ceremony, which occurs at one week of age, field and village assistants visited mother and infant pairs on alternate days to collect anthropometric measures. From this data set, I use measurements from target ages to calculate averages at 10 days (time "0"), 3, 6, 9, and 12 months, where data was available. The postnatal measurements taken are described in **Table M5**.

Table M 3: Month of birth by sex

Month of Birth	**Female n**	**Male n**
January	9	13
February	16	11
March	14	6
April	10	5
May	7	9
June	5	11
July	6	9
August	4	8
September	4	6
October	6	6
November	6	5
December	3	7
Total	90	97

Table M 4: Village by sex

Village	**Female n**	**Male n**
Baja	5	3
Jali	3	7
JannehKunda	6	6
Jattaba	2	2
Jiffarong	7	15
Joli	4	5
Kantong Kunda	3	7
Karantaba	4	3
Kemoto	2	3
Keneba	23	14
Kuli Kunda	10	11
Mandi	1	0
Manduar	8	5
Nyorro Jattaba	9	8
Sandeng	1	0
Sankandi	2	4
Tankular	4	10
Total	94	103

Table M 5: Lists the different postnatal growth measures taken, their abbreviations, and the frequency of the measurements.

Postnatal Growth Measure	**Acronym**	**Frequency of Measure**
Weight	--	

Height	--	Every other day, when possible. Averaged calculated at 10 days and 3, 6, 9, 12 months.
Head Circumference	HC	
Knee Heel Length	KH	
Mid Upper Arm Circumference	MUAC	
Triceps Skin Fold	TSF	

For postnatal growth measures, two different calculations of z-scores were included: WHO and KEN. "WHO" z-scores are calculated against data gathered from the World Health Organization's (WHO) Multicentre Growth Reference Study (MGRS), which consists of a pooled sample from six participating countries: Brazil, Ghana, India, Norway, Oman, and the United States (N=8,500). The MGRS study is described in de Onis et al. (2004). WHO z-scores were calculated using the WHO-Anthro software package (SAS/SPSS, version 3.2.2, 2011 Geneva, Switzerland), which includes an anthropometric calculator and individual assessment.

Keneba (KEN) z-scores compare the growth of the study cohort to growth averages within Gambia. KEN z-scores are available only for postnatal measures, but WHO z-scores are available for both pre- and postnatal measures.

Fetal Hair Cortisol:

Hair samples were collected at infant naming ceremonies (one week of age). The infant's entire head is washed with soap and water and shaved in ritual practice. Field and village assistants in attendance collected the hair and stored it in labeled, paper envelopes until samples could be shipped to the lab. As hair is a stable reservoir for cortisol, samples were stored at room temperature until processing.

Approximately 10 mg of hair was weighed (average hair weight = 10.12 ± 0.38) and placed into Eppendorf tubes. Hair was washed three times in isopropanol and dried under a

stream of air in a fume hood. Hair was ground using a ball mill (Retsch Mill400MM, Verder Scientific, Inc., Newton, PA, 18940) with one stainless steel ball per tube, for 10 minutes. If hair was not sufficiently ground, the sample was processed for an additional few minutes. Samples were then incubated overnight in 1 mL of methanol on a shaker (~100 rpm). Following incubation, samples were centrifuged and supernatant removed and transferred to a clean Eppendorf tube. Supernatant was evaporated using a micro-vap (Organomation, Berlin, MA 01503) and a stream of nitrogen air for ~13 minutes. Samples were then reconstituted with 0.5 mL EIA buffer solution. Samples were stored at -20°C until processing. The protocol for extraction is provided in Appendix B.

To quantify cortisol concentrations, enzyme-linked-immunosorbent assays (ELISA) were run using commercially available kits (Salimetrics Inc., State College, PA, 16803) previously validated for use in measuring cortisol in human hair (Hoffman et al., 2016a). Inter-assay coefficient of variation (CV) was 4.9% and intra-assay CV ranged from: 3.6-5.2%. Results were converted from ng/mL to dry units: ng/mg of hair.

Statistics:

Data Treatment: Following collection of postnatal growth data, averages of growth measures were calculated based on data from the week the infant turned the target age. For example, data used for growth at 3 months of age consists of an average of four measurements taken between 88-95 days of age. If data were missing, calculations were made on the most available data, unless completely absent, in which case growth measures at that age were considered missing.

While fHCCs were normally distributed, all measured data were $\log_{10}$ transformed in order to correct for any non-normal distributions in growth measurements, and to provide a

measure of control as the data used in modeling includes various units (e.g., cm, kg, ng/mg, etc.). Additionally, preliminary analyses showed categorical seasonality (i.e., wet vs. dry season of birth or conception) yielded no significant effects, so month of birth was used in its place. Months July – November were considered wet, and December – June were considered dry.

For maternal sociodemographic data, SES was calculated based on number of livestock and species type, possession of cart (which only three women had), maternal education, and household size. Each component was assigned a value and totaled to provide an SES score (**Table M6**). A distribution was made based on these scores and SES category was determined based on the resulting quartiles. These factors and assigned values were based on the American Psychological Association's definition of socioeconomic status ("SES is an economic and sociological combined total measure of a person's work experience and of an individual's or family's economic and social position in relation to others, based on income, education, and occupation."), previous research that has suggested effects of maternal education and household crowding (Reeb et al., 1987; Sheehan, 1998), and discussions of the value and importance of livestock species in Gambia (International Livestock Center for Africa Report, 1980). SES was the preferred effect to test in models, however, if independent factors used in the SES calculation (e.g. "crowding ratio," which described the number of people per household) had a stronger effect, they were included instead. The details of this calculation are provided in the **Table M6**.

Table M 6: Shows the point system used to calculate SES score within this cohort. Once calculated, SES category was determined based on quartile range. SES could be scored negatively if the crowding ratio was greater than other assets.

Factors	**Score:**
Livestock	
Sheep	+3
Goat	+2
Cow	+8
Possession	

Cart	+15
Livestock + cart = "Proxy Wealth"	This is a summarized point-number of livestock and cart
Sociodemographic:	
Family Size	if number of people living in rooms is greater than two: -1, if less than or equal +1
Education	+ total years of education (English and Arabic)
SES Scores:	Range -1-54
Low	-1 to 2 (n=58)
Mid	2 to 11 (n=75)
High	11-54 (n=42)

Statistics**:** All statistical tests and analyses were performed in JMP13 (Version 13, SAS Institute Inc., Cary, NC). Due to the numerous possible inputs and effects on infant outcomes, stepwise regression analysis was used to identify significant contributing factors to the investigated outcome prior to model building. All possible inputs are listed in **Table M7**. Sex was analyzed for each model and, if it were found to have an effect, separate models were constructed for explaining male and female infant outcomes. Once significant effects in the stepwise model were identified, fit least squares models or mixed models for longitudinal data (and repeated measures) were run and refined. It is important to note that not all factors retained in the new fit/mixed models were independently significant. These results are presented and the directional effect of factors (e.g. positive/negative) within each model is described.

Table M 7: Describes all possible factors that were included in stepwise models. Presented models were built using only significant factors from these analyses.

Information input into Stepwise Models	
Category	Input Details

Maternal	Years of school Arabic or English; Total years Education; Children Alive, Dead, Stillborn, Micarried, or Lost; Parity; Number of rooms lived & slept in; Numberof people living in rooms; Crowding ratio; Number of sheep, goats, or cattle; Number of livestock; Cart possession; Proxy wealth; SES category; Maternal age; Maternal height; Maternal change in weight (summarized in Table M1)
Environmental	Month of birth, village, season of conception, season of birth
Birth Outcome	fHCC, birth weight, & gestational age

For prenatal models there was high and general collinearity between the prenatal growth measures, so each was treated as a separate outcome and were not used to model each other in order to reduce redundancy and avoid masking other effects. Several of the prenatal growth models have a relatively low R-squared values, but are significant, suggesting that they explain a low amount of the variation among individuals in prenatal growth measurements, but that the included factors are contributing significantly to outcome. Lastly, models were only constructed by sex if a significant effect was found.

All postnatal growth measurements and z-scores were modeled for each sex independently as differences in male and female growth trajectories have been well established. Mixed models were constructed and evaluated for each physical growth measurement and z-scores, which were constructed both for a global population comparison (WHO) and within Gambia (KEN). As with the prenatal models the factors included in SES calculation were used independently if they had a greater impact on outcome (e.g. education, wealth, and family/household size), otherwise SES score was the preferred input. For all models,

identification, "ID," and time were used as random variables to account for variation due to repeated and longitudinal measures. R-squared values are reported for each model along with effect estimate, error, and p-value.

Additional descriptive statistics and relationships for fHCC are provided, regardless of significance, as so little has been described or characterized about its expression in these contexts. If it was determined that post hoc analyses were needed to better understand effect relationships to the investigated outcome, analysis of variance (ANOVA) and Tukey Kramer honestly significant different (HSD) tests were used as appropriate. fHCC category was used to conduct post-hoc analysis to determine if infants with low, mid, or high-range fHCC had different outcomes. Categories were defined using quartile ranges and are defined in the following table:

Table M 8: Description of fetal hair cortisol categories, ranges, and quartile distributions.

fHCC Category	Range (ng/mg)	Quartile Range (0-100%)
Low	0.02-0.14	0-25%
Mid	0.14-0.26	25-75%
High	0.26-0.74	75-100%

These results are described in each section, as appropriate, and indicated on the corresponding graphs (symbols: $p \leq 0.05$ = *; $p \leq 0.01$ = **; $p \leq 0.001$ = ***).

Results

Model results are presented in the following order: birth outcome including fHCC, gestational age, birth weight; prenatal growth, and postnatal growth, including body, head, and limb measurements. Significant effects in the models are summarized in **Table R2**. Detailed statistical tables from models are provided in Appendix C (C.1 – Birth Outcomes, C.2 – Prenatal Growth, C.3 – Postnatal Growth), and referenced in numerical order in text. In all figures, females are presented on the left-hand side, and males on the right.

Prenatal growth:

There were no significant differences or effects found in prenatal growth measures between dry and wet season of birth or conception; however, month of birth was still used as a possible effect as it can inform the season of development (e.g. an infant born in December would have been *in utero* during the majority of the wet season in The Gambia). Models were analyzed by sex only where there was an effect or difference seen. The results of prenatal growth models for physical measurements and WHO z-scores are presented below, again KEN z-scores are not available for prenatal data.

Body Measures:

Crown Rump: The model for crown rump length (R^2=0.47, p<0.0001) is strongly influenced by birth weight (p<0.0001) and month of birth (p=0.001). Additional contributing factors were: village, maternal height, SES, and fHCC, although not independently significant (Table C5). The effect of SES is driven by differences individuals in the “mid” category (p=0.05). Village and fHCC are negatively associated with crown rump measures.

Abdominal Circumference (AC): The model for AC (R^2=0.21, p=0.0003) includes birth weight (p=0.0007), maternal years of education (p=0.04), proxy wealth (p=0.04), and the "lost a child" category (p=0.009) as significant effects, and nonsignificant effects: maternal height and fHCC (Table C6).

The initial model for associated z-scores suggests a differential effect on sexes and was modeled separately for males and females. The model for female AC z-scores was not significant (R^2=0.32, p=0.35), but included total years of education (p=0.05) as a significant effect and "lost a child," village, and birth weight as additional contributors. Education and birth weight are negatively associated with female AC Z-scores. The model for male AC z-scores is significant (R^2=0.2, p=0.05), but does not include birth weight. This model included the same inputs as that for AC measurements. Proxy wealth (p=0.02) and total education (p=0.015) were significant, and "lost a child" category, crowding ration, and month of birth were retained. Here October births are positively associated with male AC Z-score (p=0.026) and proxy wealth, education, and crowding ratio are negatively associated.

Tibia Length (TL): The model for physical measures of TL (R^2=0.26, p=0.05, see Table C13) show parity (p=0.003) and crowding ratio (p=0.04) are significant effects, while birth weight, maternal height, and SES contribute. Low SES category has a slight, positive effect on TL measures (p=0.01).

Femur Length (FL): Both FL physical and z-score measures were modeled by sex (Table C14 and C15). The models for male FL are stronger. For physical measures of female FL (R^2=0.35,

p=0.5), no significant effects were identified, but maternal education, village, month of birth, and fHCC were used to construct the best model. The model for male FL measures (R^2=0.39, p=0.08) show fHCC (p=0.003) and SES (p=0.05) are significant effects; nonsignificant contributors include: parity, height, month of birth, gestational age, and birth weight. The effect of fHCC has a negative effect on female FL and a positive effect on male FL.

The models for FL z-scores are stronger than those for physical measures and significant (R^2_{female}=0.43, p=0.04; R^2_{male}=0.42, p=0.03, see Table C15). For female FL Z-scores birth weight (p=0.03) and "lost a child" category (p=0.04) are significant, negative effects on outcome. Additional contributors are: maternal height, education, and village. For male FL Z-scores, fHCC (p=0.003) and SES (p=0.01) had significant effects, and with birth weight, village, month of birth, parity and height retained in the model. fHCC has a strong positive effect on male FL Z-scores.

Head Measures:

Occipitofrontal diameter (OFD): Both physical and z-score OFD data were modeled by sex (Table C8 & C9). Female OFD measures are best explained (R^2=0.46, p=0.01) by birth weight (p=0.002), month of birth with May and August showing negative effects on OFD measures, SES, maternal height, and parity. Height, parity, and SES, overall, had negative effects of OFD measures, but low SES was positively correlated (p=0.06) with female OFD measures. The model for males was not significant, but does capture 50% of variation, (p=0.13). Birth weight (p=0.01) and parity (p=0.003) are significant effects on male OFD measures, along with nonsignificant contributors: village, maternal height and month of birth. Village effects were differential depending on location (Table C8).

The models for the associated z-scores (R^2_{female}=0.32, p=0.26; R^2_{male}=0.73, p=0.06) show differential strength, the model for male OFD z-scores explain a greater amount of variation and nears significance (Table C9). The female model shows no significant effects, but includes birth weight, SES, height, parity, and month of birth. For male OFD z-scores, birth weight (p=0.003), proxy wealth (0.007), crowding ratio (p=0.016) have significant effects. Education, maternal height, village, and month of birth also contribute.

Biparietal Diameter (BPD) Z-score: This model (R^2=0.38, p=0.04, see Table C10) shows that birth weight (p=0.009), proxy wealth (p=0.01), total education (p=0.03) have significant effects, while parity, village, and month of birth also contribute. Keneba (p=0.03) and Manduar (p=0.01) both have negative effects on BPD z-score, while April (0.008) and February (0.005) births have positive associations with BPD z-scores.

Head Circumference (HC): The model for HC measures (R^2=0.31, p=0.002, see Table C11) showed birth weight (p=0.0003) and crowding ratio (p=0.023) are significant, followed by SES and "lost a child" category. The effect of SES was driven by difference in mothers in low SES and had a positive correlation with HC (p=0.06). "Lost a child" category had a negative effect on HC values, unlike the relationship this factor had with various body measurements. The model for HC z-scores reveal no significant effects (R^2=0.22, p=0.26), but do show that fHCC was negatively associated with HC z-score (Table C12).

Summary: These models for prenatal growth, overall, explain less than 50% of the variation in the data set; they highlight that maternal sociodemographic factors, environment, and, for femur length, fetal hair cortisol play a significant role in these outcomes.

Birth Outcome:

Fetal Hair Cortisol:

Basic descriptive statistics were run to characterize fHCC expression. Fetal hair cortisol values range from 0.023-0.64 ng/mg (n=204). No significant differences were found between sexes, season of birth or conception, or among SES categories (**Table R1**). Maternal parity is significantly different between categories, where infants born to primparous mothers have higher levels of fetal hair cortisol (p=0.047). Univariate correlation analyses between fHCC and gestational age and birth outcome did not reveal a significant relationship, but are important contributors to models of variation in fHCC.

Table R 1: Descriptive statistics of fetal hair cortisol in relation to maternal parity, socioeconomic status, infant sex, season of conception and birth. Infant fHCCs was significantly different between infants born to multiparous and primparous mothers.

Fetal Hair Cortisol - Averages				
Sex	**Raw Mean**	**Log_{10} Transformed Mean**	**n**	**p-value**
Female	0.22	-0.7	98	0.32
Male	0.2	-0.73	104	
Parity	**Raw Mean**	**Log_{10} Transformed Mean**	**n**	**p-value**
Multiparous	0.2	-0.74	176	0.047*
Primparous	0.24	-0.64	24	
SES	**Raw Mean**	**Log_{10} Transformed Mean**	**n**	**p-value**
High	0.21	-0.717	43	0.9
Mid	0.2	-0.724	58	
Low	0.21	-0.723	76	
Unknown	0.22	-0.71	24	
Season of Conception	**Raw Mean**	**Log_{10} Transformed Mean**	**n**	**p-value**
Dry	0.22	-0.69	115	0.12
Wet	0.19	-0.74	75	
Season of Birth	**Raw Mean**	**Log_{10} Transformed Mean**	**n**	**p-value**

Dry	0.21	-0.73	130	0.14
Wet	0.22	-0.68	60	

The best model for female fHCCs yielded R^2=0.31, but was not significant. Significant effects include: gestational age (p=0.001) and birth weight (p=0.1). Nonsignificant effects include parity and month of birth. The best model for male fHCC was significant (R^2=0.38, p=0.017). The only significant factor was village (p=0.04); non-significant contributing factors include: parity, maternal education, gestational age, and birth weight. These models are summarized in Table C2.

Interestingly, within the models gestational age has a positive relationship with female fHCC and a negative relationship with male fHCC. This relationship is explored further in the next section.

A second model for female fHCC expression includes maternal height and change in maternal weight during the course of pregnancy. With these included, the effect of villages also increases. Unfortunately, there is missing weight data for a number of mothers and this creates a bias in the model (R^2=0.8, R^2_{adj}=0.4, n=42; p=0.07see Table C2b), so these results are tentative. However, this model suggests that maternal weight should be included in future studies, if possible. Inclusion of maternal height and change in weight during pregnancy did not strengthen the model of male fHCCs. The model in males accounts 38% of the variation seen in fHCC expression among the study cohort, and is significant.

Gestational Age and Birth Weight:

Gestational age and birth weight outcomes were modeled by sex. Strength of factors vary in a sex-dependent. Additionally, the collinearity between gestational age and birth weight

(R=0.54) should be noted. Both are included as their relationship to fetal hair cortisol is not the same and often in the opposite direction.

For gestational age, maternal inputs varied between the sexes (Table C3). The strongest model to explain female gestational age (R^2=0.49, p=0.003), included significant effects: birth weight (p<0.0001) and fHCC (p=0.02) and nonsignificant contributors: SES and parity. The model for male gestational age (R^2=0.36, p=0.01) includes birth weight (p<0.0001) and nonsignificant effects: fHCC, "Lost a child" and village. Recall, "lost a child" refers to women who self-describe the loss of a child either as a death, stillbirth, or miscarriage. The nature and degree of effect of fHCC is differential: For females, fHCCs contribute significantly (p=0.02) and positively, while male gestational age is negatively correlated with fHCCs, although the effect was not independently significant.

Post-hoc analysis revealed that fHCCs were significantly and positively correlated with female gestational age (R=0.32, p=0.0006, see Fig. R1); in males fHCCs were negatively correlated with male gestational age (R=0.04, p=0.05). When including categorical values for fHCCs, females with high concentrations of fHCC were born at significantly later ages [p=0.008: where gestational age of high fHCC > low fHCC (p=0.006); and high fHCC > mid fHCC (p=0.07)]. Males with low fHCC are born at significantly later ages [p=0.04; where gestational age of low fHCC > high fHCC (p=0.037)].

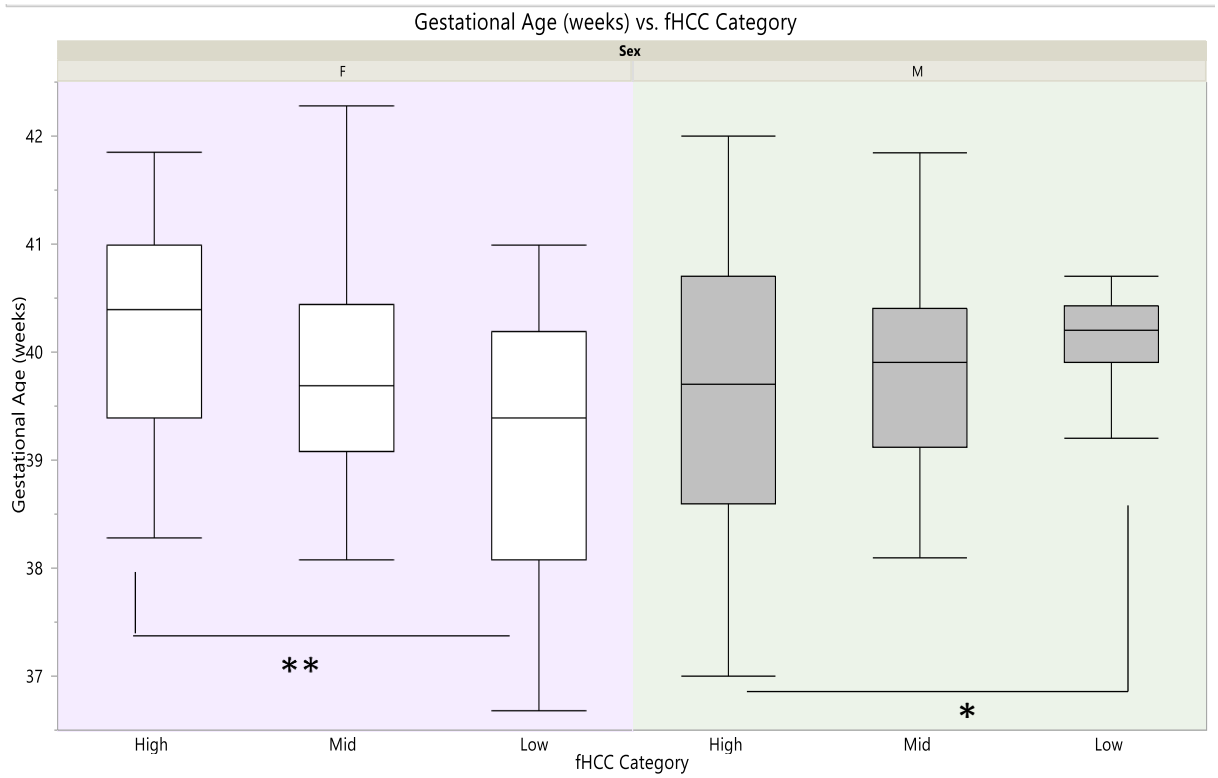

Figure R 1: Shows gestational ages by sex and fHCC category. Female gestational age has a significant positive relationship to fHCC (p=0.0006), while male gestational age has a negative relationship (p=0.05). Females with high fHCC values are born significantly later when compared to female infants with low fHCC values (p=0.006). Males with low fHCC are born at significantly later ages (p=0.037).

All factors included in the models for males (R^2= 0.68, p=0.0004) and females (R^2= 0.66, p=0.015) birth weight were the same, but the strength of influences varied (Table C4). For both males and females gestational age, as expected due to the collinearity, is the most significant factor. For females, maternal height (p=0.006) and fHCC (p=0.05) are significant effects. For male birth weight, month of birth (p=0.01) and village (p=0.08) are significant.

Postnatal Growth:

Seasonality effects were also considered by examining season of birth and conception in relation to the direction (positive or negative) effect on growth. Overall, there were no significant

differences found, however month of birth was still included as it explains significant variation and can still account for variation due to seasonality or more local effects. Both WHO and KEN z-scores are illustrated when significant to illustrate similarities and differences within the comparisons. The results of all postnatal models are presented below [Reminder: the significance of results are indicated on the corresponding graphs ($p \leq 0.05$ = *; $p \leq 0.01$ = **; $p \leq 0.001$ = ***)].

Body:

Weight: The model for female weight (R^2_{female}=0.77, Table C17), while strong did not include any independently significant effects. Contributing factors included: parity, proxy wealth, month of birth, village, and fHCC. The model for male weight (R^2_{male}=0.75, Table C17) included the following significant factors: parity (p=0.04), crowding ratio (p=0.04), village (p=0.04), and fHCC (p=0.04). For both sexes, fHCC is negatively correlated with infant weight. Post hoc analysis show that male weights differed significantly by fHCC category (p=0.002) such that infants with low fHCC weigh significantly more at 12 months than those with mid (p=0.01) or high (p=0.006) fHCCs. No significant differences were found in females (**Fig. R2**).

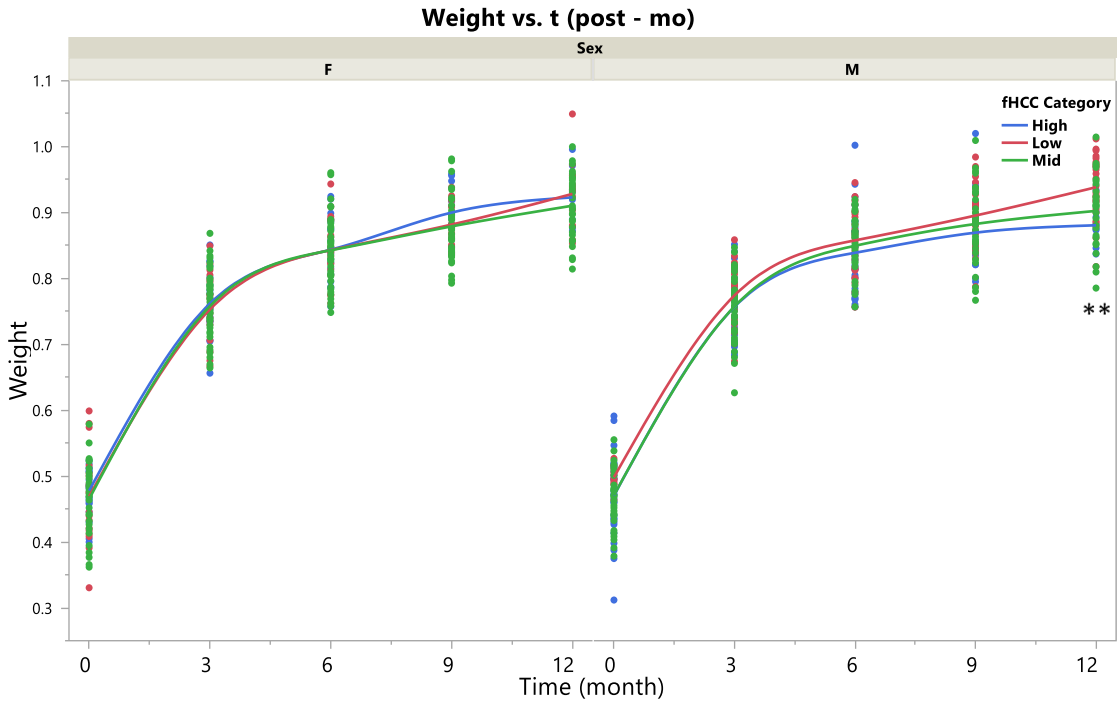

Figure R 2: Shows the trajectory of postnatal weight over time, by sex and fHCC category. Male weights differ significantly at 12 months (p=0.006), such that infants with low fHCC weigh more than infants with mid (p=0.01) or high (p=0.006) fHCC.

Models for weight for age z-scores (WAZ, Table C18) include the same respective inputs and show the same trends as the models for weight (WHO: R^2_{female}=0.69; R^2_{male}=0.75; KEN: R^2_{female}=0.68; R^2_{male}=0.75). There are no apparent differences between models constructed using WHO and KEN z-scores. WAZ varies significantly by fHCC category at 12 months (p_{WHO}=0.006; p_{KEN}=0.002) where infants with low fHCCs have significantly greater z-scores than infants with mid (p_{WHO}=0.01; p_{KEN}=0.007) and high (p_{WHO}=0.04; p_{KEN}=0.016) hair cortisol values for males. Additionally, differences in male z-scores at time "0", which consist of measurements collected from when the infant was 10 days old, and fHCCs trend towards significant (p=0.07). Despite the visual appearance of a difference at 9 months in female weight for age z-scores (WAZKEN, **Fig. R4**), there is no statistically significant difference among

fHCC categories at this time point. This may be due to the small sample size of high fHCC females with a WAZ/WAZKEN scores at this time point (n=10).

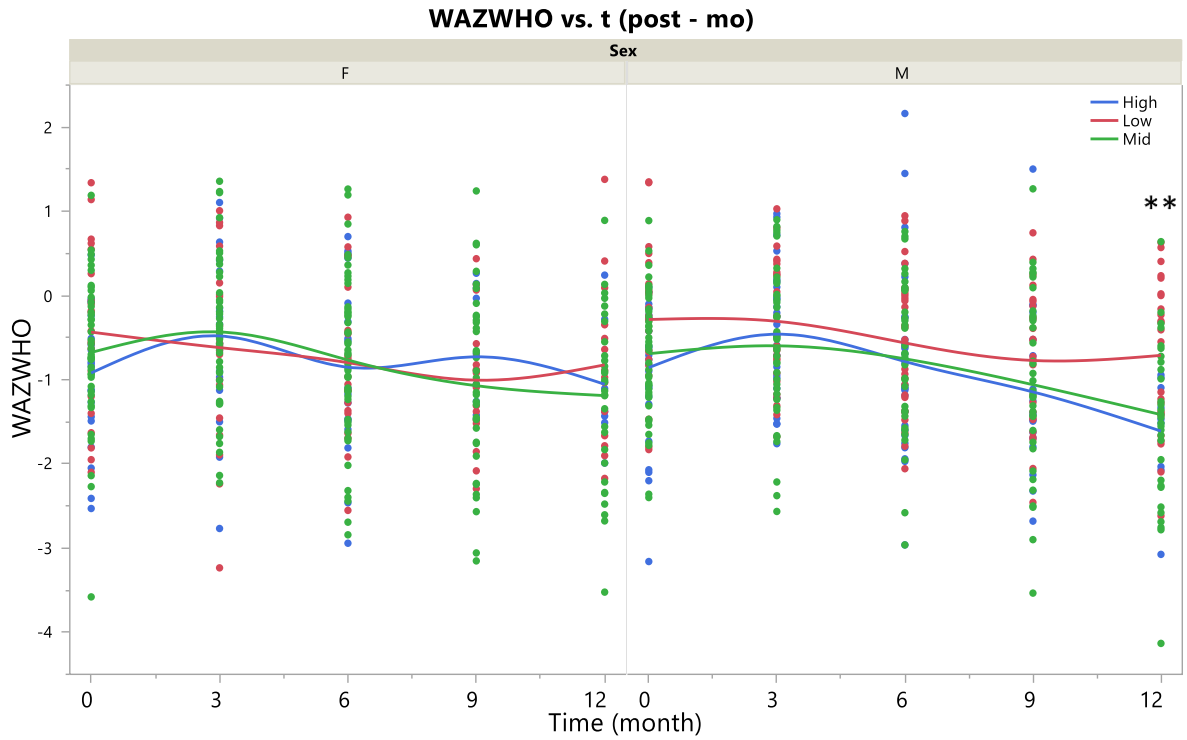

Figure R 3: Shows the trajectory of postnatal weight for age WHO z-scores over time, by sex and fHCC category. Male weight for age z-scores differ significantly at 12 months (p=0.006), such that infants with low fHCC weight more than infants with mid (p=0.01) or high (p=0.007) fHCC. The difference between low fHCC infant weight for age z-scores and other mid- and high fHCC categories at birth trend towards signficant (p=0.07), such that males with low fHCCs weight more.

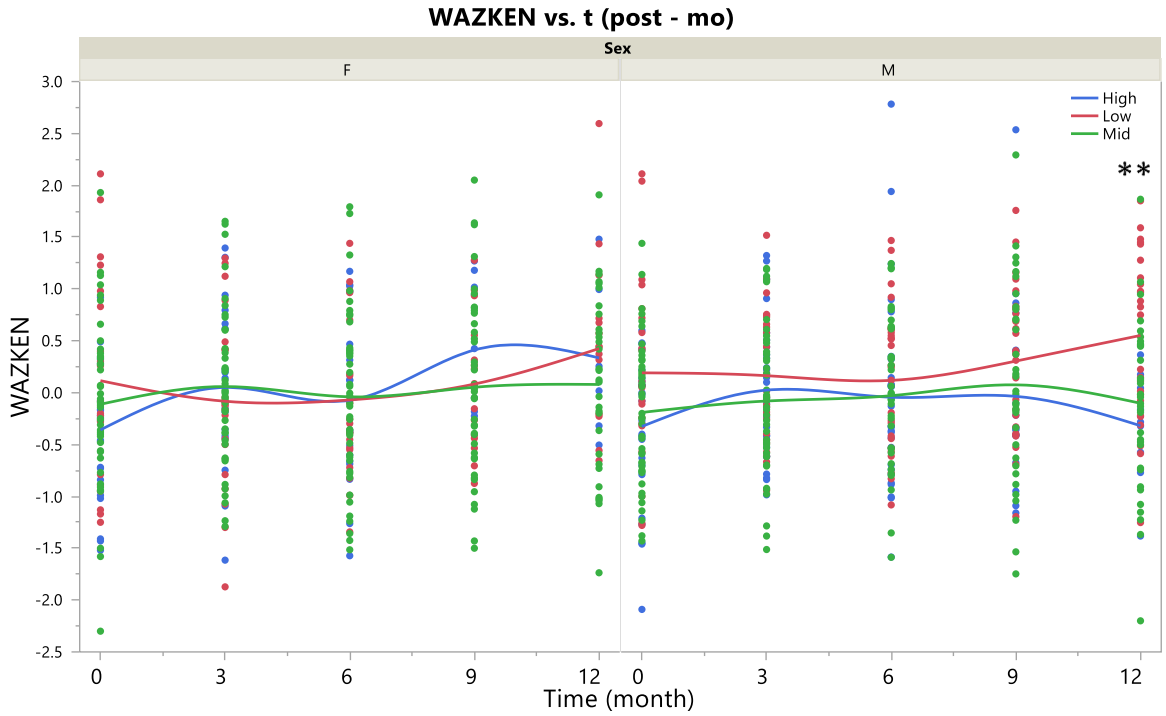

Figure R 4: Shows the trajectory of postnatal weight for age KEN z-scores over time, by sex and fHCC category. Male weight for age z-scores differ significantly at 12 months (p=0.002), such that infants with low fHCC weigh more than infants with mid (p=0.006) or high (p=0.01) fHCC.

Height: Height measures were poorly modeled by the data available in this study; all models produced yielded negative r-squared values, even if effects were significant. The best of these models are summarized in Table C19. Height for age z-scores were modeled better by the available data (WHO: R^2_{female}=0.67; R^2_{male}=0.66; KEN: R^2_{female}=0.67; R^2_{male}=0.66). There were no large differences between WHO and KEN female HAZ models, but the strength of effects are variable. The female HAZ models included one significant effect: birth weight (p_{WHO}=0.0007; p_{KEN}=0.02), while SES and village contributed. For males, use of KEN z-scores shows that crowding ratio (p=0.03) has a significant relationship with height for age z-scores, while WHO z-scores show significant effects of month of birth, where October (p=0.03) and November (p=0.01) have positive effects on height for age z-scores (Table C20). Village (p_{WHO}=0.08;

p_{KEN}=0.06), birth weight (p_{WHO}<0.0001; p_{KEN}<0.0001), and fHCC (p_{WHO}=0.16; p_{KEN}=0.04) were included.

Fetal hair cortisol is negatively associated with male HAZ. Post hoc analyses using KEN z-scores show male height is significantly different at 12 months of age (p=0.04), where infants with lower fHCCs have higher HAZ than those with mid-range concentrations (p=0.05). Despite a lower z-score average than infants with mid fHCCs, male infants with high fHCCs do not have significantly different HAZ; this is likely due to a small sample size.

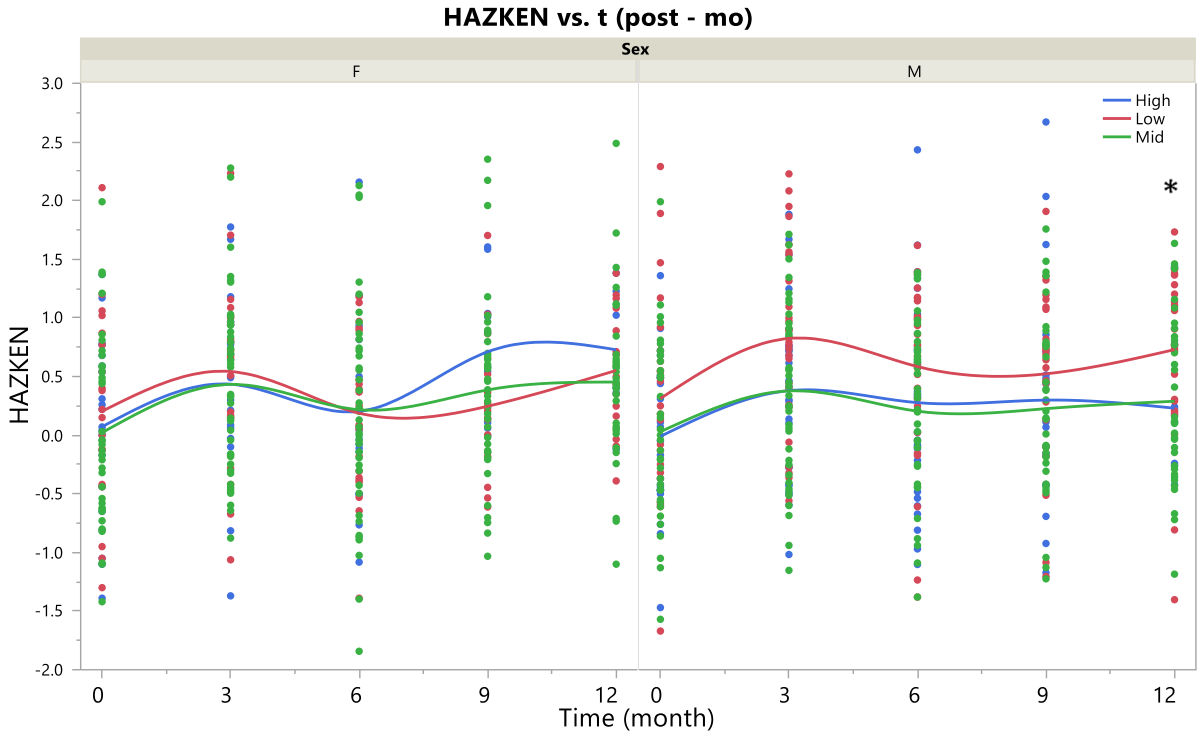

Figure R 5: Shows the trajectory of postnatal height for age KEN z-scores over time, by sex and fHCC category. Male height for age z-scores differ significantly at 12 months (p=0.04), such that infants with low fHCC are taller than infants with mid-range fHCC (p=0.05).

Weight for Height Z-scores (WHZ): The best model for WHZ for females (WHO: R^2_{female}=0.57; KEN: R^2_{female}=0.55) did not include any independently significant factors, but the following were retained: parity, SES, month of birth, village, and fHCC. Parity, month of birth, and fHCC

category were all negatively associated with female WHZ z-scores (Table C21). The best model for males (WHO: R^2_{male}=0.6; KEN: R^2_{male}=0.58) included the following significant factors: village (p_{WHO}=0.05; p_{KEN}=0.03), and fHCC (p_{WHO}=0.07; p_{KEN}=0.03), and retained: crowding ratio and month of birth. Crowding ratio, SES, and fHCC were all negatively associated with male WHZ z-scores, while village effects were differential depending on location (Table C21).

Additional analyses showed a significant difference in male WHZ z-scores at 12 months (p_{WHO}=0.02; p_{KEN}=0.008) such that male infants with low fHCCs have greater z-scores than those with mid (p_{WHO}=0.05; p_{KEN}=0.03) and high (p_{WHO}=0.04; p_{KEN}=0.02) fHCCs.

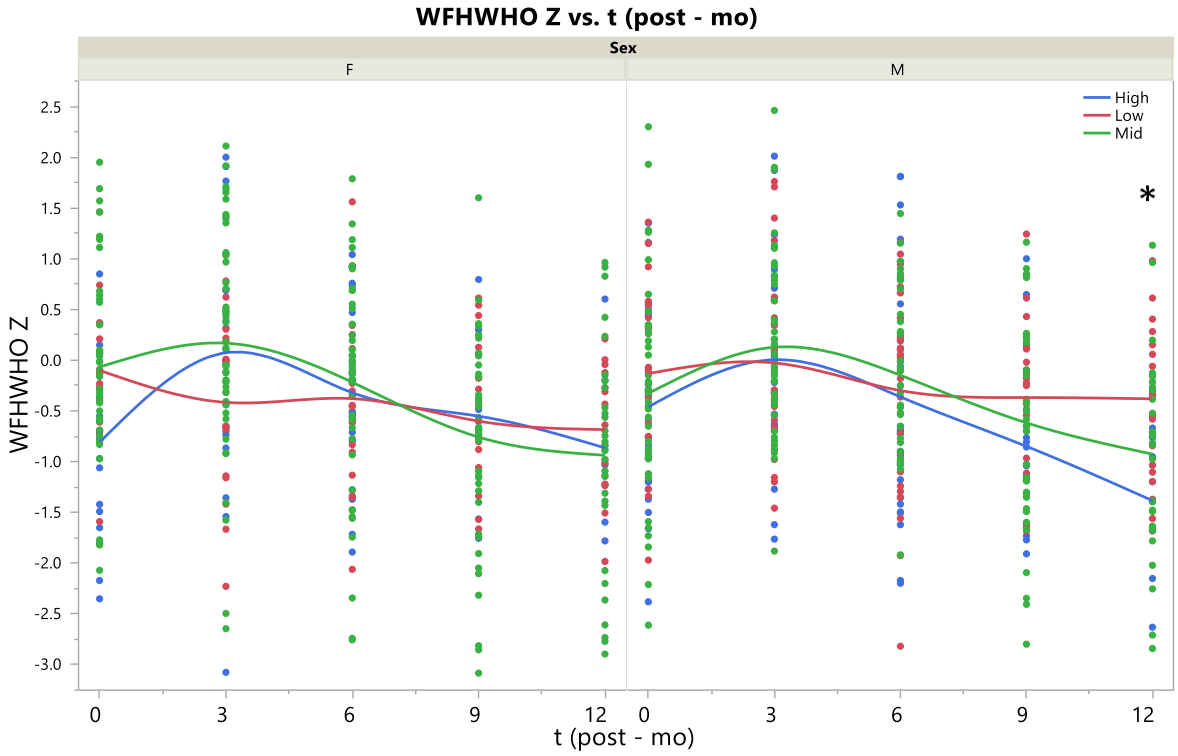

Figure R 6: Shows the trajectory of postnatal height for age WHO z-scores over time, by sex and fHCC category. Male weight-for-height WHO z-scores differ significantly at 12 months (p=0.02), such that infants with low fHCC have greater scores than infants with mid-range (p=0.05) and high (p=0.04).

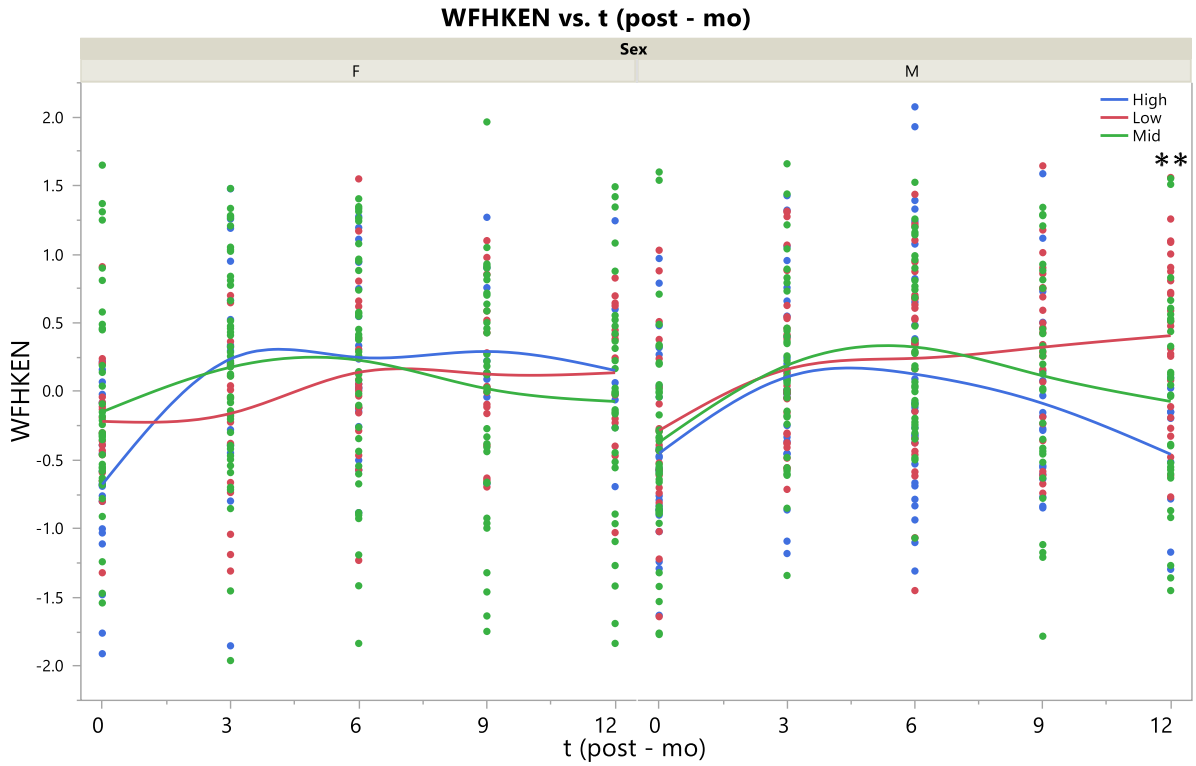

Figure R 7: Shows the trajectory of postnatal height for age WHO z-scores over time, by sex and fHCC category. Male weight-for-height KEN z-scores differ significantly at 12 months (p=0.008), such that infants with low fHCC have greater scores than infants with mid-range (p=0.03) and high (p=0.02) fHCC.

Head:

Head Circumference (HC): The model for female HC (R^2_{female}=0.85) shows that total years of education (p=0.005) and infant birth weight (p=0.05) contribute significantly to HC outcome. Additionally, parity, month of birth, village, gestational age, and fHCC were retained in the model, although none were significant. Male HC measurements (R^2_{male}=0.86, Table C22) are significantly predicted by birth weight (p=0.001) and village contributed (p=0.06). Additionally, SES, month of birth, gestational age, and fHCC were included, although not independently significant. Village effects have an overall negative relationship to both male (Keneba, p=0.007) and female (Manduar, p=0.04) HC measures (Table C22).

Post hoc analyses revealed significant differences in male HC according to fHCC category at 3 (p=0.03) and 6 (p=0.01) months of age. At 3 months, male infants who were with high concentrations of fetal hair cortisol had significantly smaller HC measures compared to male infants with mid-range fHCCs (p=0.03). At 6 months, HC measures of male infants with high fHCCs were significantly smaller than infants with both mid (p=0.02) and low (p=0.04) fHCCs (**Fig. R 8**). This trend continues into later ages, but is not statistically significant.

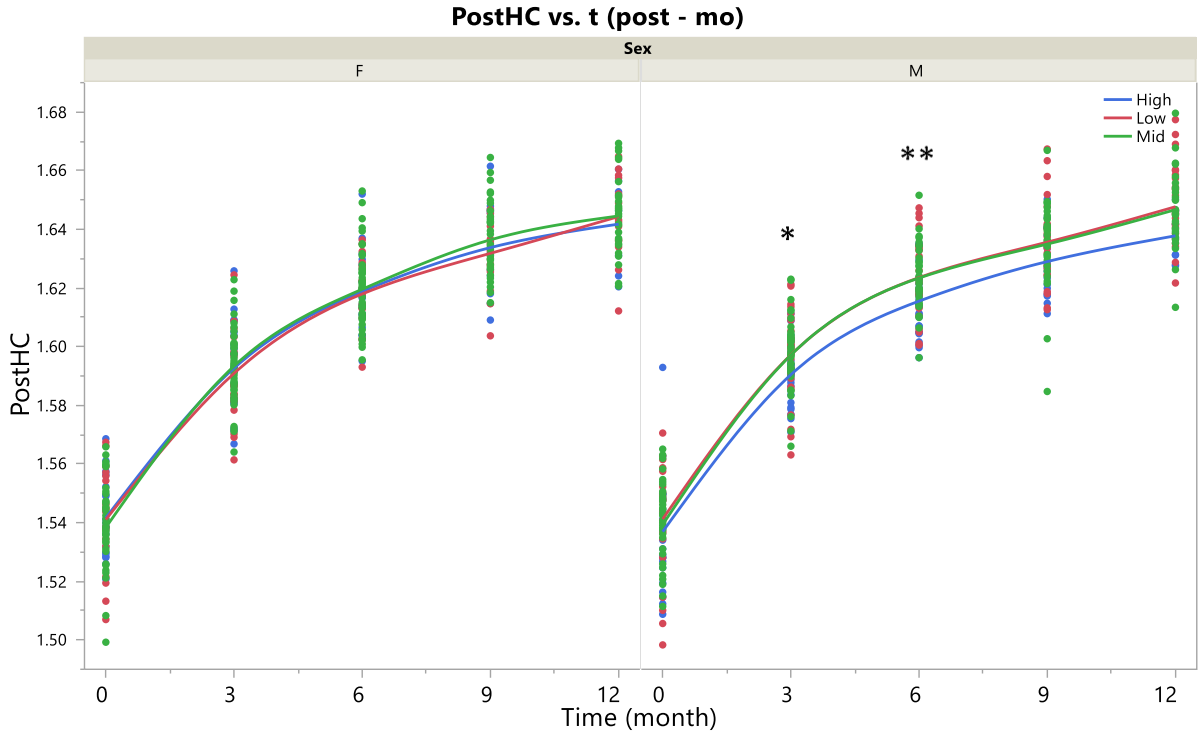

Figure R 8: Shows the trajectory of postnatal HC growth over time, by sex and fHCC category. Male HC measurements differ significantly at 3 (p=0.03) and 6 months (p=0.01). At 3 months, male infants who were with high fHCCs had significantly smaller HC measures compared to male infants with mid-range fHCCs (p=0.03). At 6 months, HC measures of male infants with high fHCCs were significantly smaller than infants with both mid (p=0.02) and low (p=0.04) fHCCs.

HC z-scores (HCZ) retained the same factors as the model for physical measurements (Table C23). The best models for female HCZ (WHO: R^2_{female}=0.76; KEN: R^2_{female}=0.71) includes the following nonsignificant factors: SES, parity, village, month of birth, birth weight,

and fHCC. The primary difference between the WHO and KEN HCZ models lies with the direction of association of the Manduar village effect: WHO HCZ show a positive association while KEN HCZ show a negative one of almost equal strength.

For males, HCZ are best modeled (WHO: R^2_{male}=0.78; KEN: R^2_{male}=0.71) by birth weight (p_{WHO}=0.002; p_{KEN}=0.001), and the following nonsignificant factors: crowding ratio, parity, village, month of birth, and fHCC. Crowding ratio has a negative relationship to male HCZ. For both males and females, the strongest individual predictor of postnatal HCZ was birth weight, although not significant for females.

Post hoc analyses showed that male KEN HCZ differed significantly by fHCC category at 6 months (p=0.04), such that infants with high fHCCs were significantly lower than those with mid-range fHCCs (p=0.04) (**Fig. R9**).

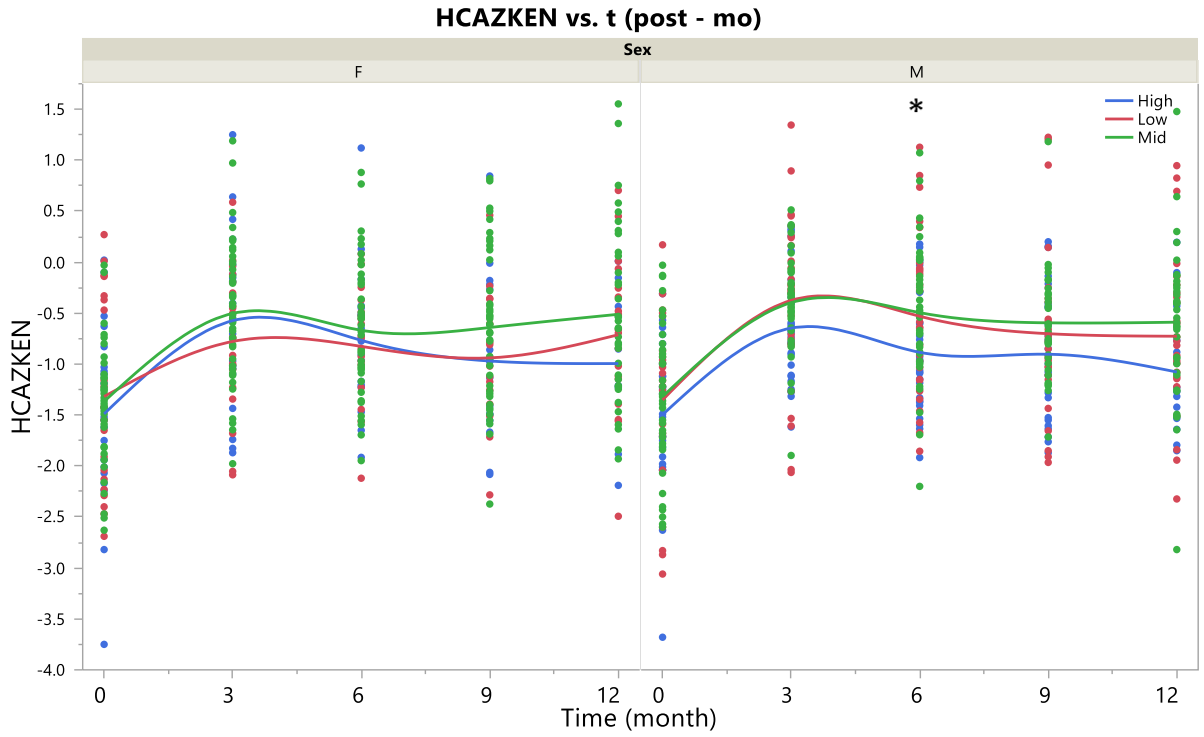

Figure R 9: Shows the trajectory of postnatal HC KEN z-score over time, by sex and fHCC category. Male HC KEN z-scores differ significantly at 6 (p=0.04), such that infants with high fHCCs had significantly smaller HC measures compared to male infants with mid-range fHCCs (p=0.04).

Limbs:

Knee Heel (KH) length: Overall, models for KH lengths were similar between the sexes (R^2_{female}=0.86; R^2_{male}=0.88, see Table C24). The model for female KH lengths did not include any maternal factors, but did include birth weight (p=0.003), village and fHCC, although not significant. Village effects on female KH lengths were variable in their association (Table C24). Male KH lengths were best modeled by birth weight (p=0.0002), village, SES and fHCC. As with head circumference, the best sole predictor of the KH length was birth weight.

Post hoc analyses showed a significant difference in female KH lengths at time "0" (p=0.03). Female infants with high fHCCs have greater KH measures compared to those with mid-range fHCCs (p=0.05). No significant effects were found in males, but fHCC does show an overall negative association with KH length in males.

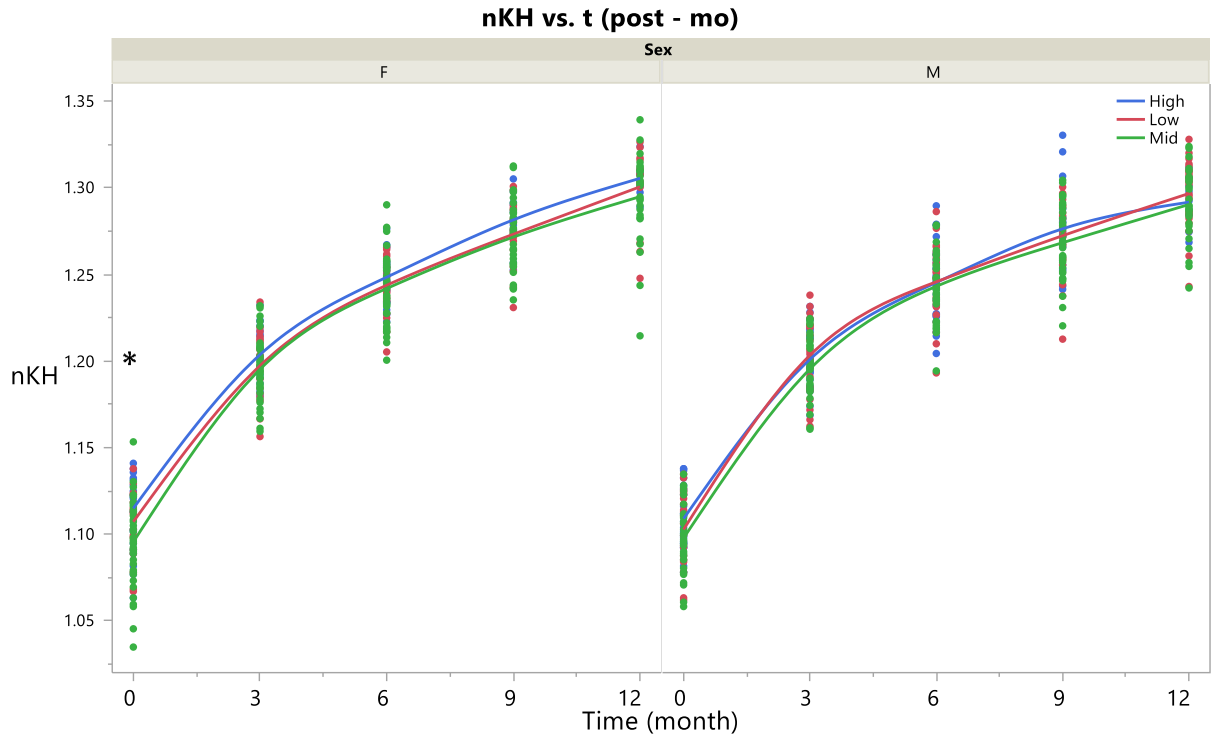

Figure R 10: Shows the trajectory of postnatal KH length over time, by sex and fHCC category. Female KH lengths differ significantly at time 0 (p=0.03), such that infants fwith high fHCCs have greater KH lengths compared to female infants with mid-range fHCCs (p=0.05).

Mid-Upper Arm Circumference (MUAC): Female MUAC measurements are best modeled (R^2_{female}=0.52), significantly, by birth weight (p=0.02) and, not significantly, SES, parity, village, and fHCC. The best model for male MUAC (R^2_{male}=0.6) included SES (p=0.05), parity (p=0.01), village (p=0.01), birth weight (p=0.002), and, not significantly, month of birth and fHCC. Low SES had a negative relationship to male MUAC scores (p=0.03); village and month of birth effects were variable, while Keneba had a negative effect (p=0.002) (Table C25).

Post hoc analyses revealed a significant difference in male MUAC measurements by fHCC category at 12 months (p=0.01), such that male infants with low fHCC measures have higher MUAC measurements when compared to infants with high (p=0.04) or mid (p=0.04) range fHCCs.

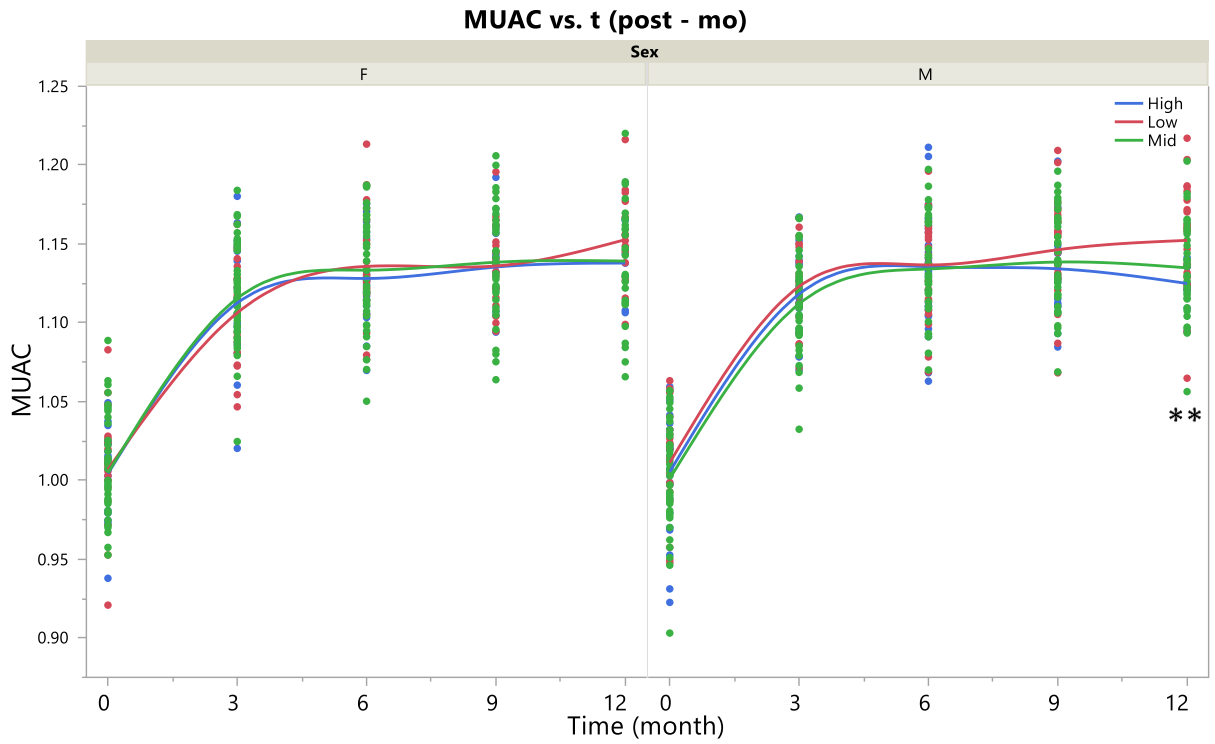

Figure R 11: Shows the trajectory of MUAC growth over time, by sex and fHCC category. Male MUAC measurements differ significantly at 12 months (p=0.01), such that infants with low fHCC have greater MUAC measures than infants with mid-range (p=0.04) and high (p=0.04) fHCC.

The best models for MUAC z-scored (MAZ) differed between the WHO and KEN data sets. For females, the model for KEN included village and gestational age. For males, the differences were less apparent between WHO and KEN models. For both males and females, the models using WHO MAZ explain a greater degree of variation in the data (Table C26).

The models for female MAZ (WHO: R^2_{female}=0.9; KEN: R^2_{female}=0.5) include parity (p_{WHO}=0.04; p_{KEN}=0.07) and birth weight (p_{WHO}=0.5; p_{KEN}=0.001) and the following nonsignificant factors: SES and fHCC. In addition to these factors, the model for female KEN MAZ included village, which was not significant, and gestational age (p=0.008).

The models for male MAZ (WHO: R^2_{male}=0.8; KEN: R^2_{male}=0.53) include village (p_{WHO}=0.23; p_{KEN}=0.04) and birth weight (p_{WHO}=0.04; p_{KEN}=0.01) and the following

nonsignificant factors: SES, parity, and fHCC. In addition to these, the model for male WHO MAZ include month of birth, although not significant. Again, Keneba had a negative effect (p_{WHO}=0.01; p_{KEN}=0.03).

Post hoc analyses revealed a trending difference among female MUAC z-scores by fHCC category at birth (p_{KEN}=0.08), and significant differences at 12 months in male MUAC scores by fHCC categories (p_{WHO}=0.03; p_{KEN}=0.02), where males with low fHCCs have greater MUAC z scores than males with mid- (p_{WHO}=0.04; p_{KEN}=0.03) and high range (p_{KEN}=0.07, trending).

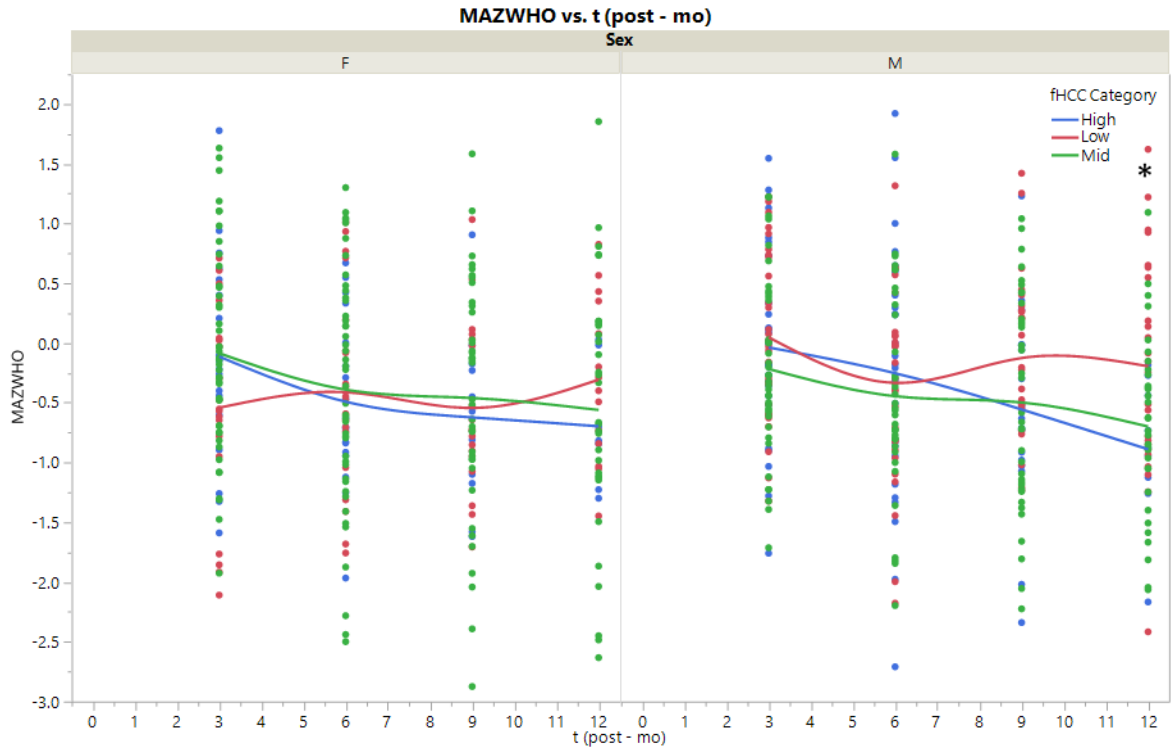

Figure R 12: Shows the trajectory of MUAC growth over time, by sex and fHCC category. Male MUAC measurements differ significantly at 12 months (p=0.03), such that infants with low fHCC have greater scores than infants with mid-range (p=0.04).

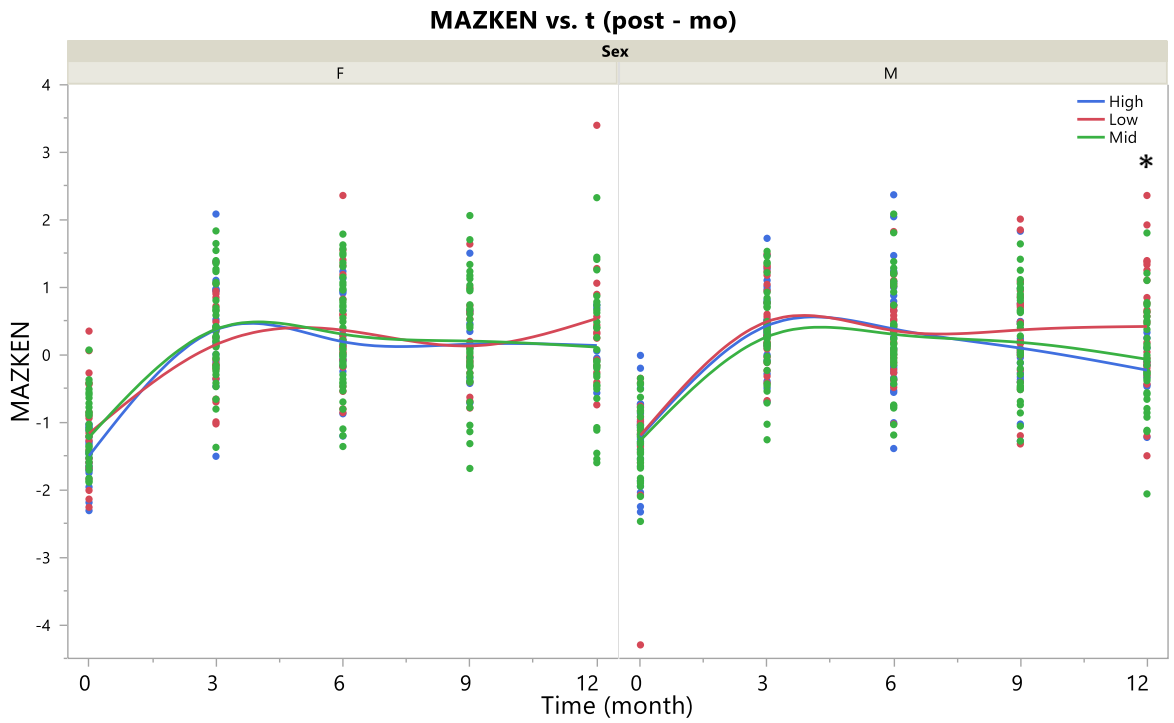

Figure R 13: Shows the trajectory of MUAC growth over time, by sex and fHCC category. Male MUAC measurements differ significantly at 12 months (p=0.02), such that infants with low fHCC have greater scores than infants with mid-range (p=0.03) and trend towards significance when compared to high fHCC (p=0.07). Differences between categories trend towards significance at 0 months (p=0.08).

Triceps Skin Fold (TSF): Measures of TSF for females are best modeled (R^2_{female}=0.45) by gestational age (p=0.004) and the following: SES, village, and fHCC. Low SES (p=0.06) and gestational age have slight, negative relationships with female TSF measures. Male TSF measures are best modeled (R^2_{male}=0.45) by parity (p=0.03) and village (p=0.06) and the following factors, which are not independently significant: SES, month of birth, birth weight, and fHCC.

Models for TSF z-score do not vary greatly between WHO and KEN scores in terms of included effects, however, models for WHO scores were overall stronger, but the significance of individual effects are variable between WHO and KEN comparisons. Female TSF scores are best modeled (WHO: R^2_{female}=0.79; KEN: R^2_{female}=0.46) by parity (p_{WHO}=0.1; p_{KEN}=0.03), gestational

age (p_{WHO}=0.004; p_{KEN}=0.005), while village, birth weight, and fHCC (p_{WHO}=0.3; p_{KEN}=0.9). Additionally, SES is included in models of WHO z-scores, although not independently significant.

The male TSF z-score models (WHO: R^2_{male}=0.76; KEN: R^2_{male}=0.43) did not include any independently significant effects, but both retained: SES, village, month of birth, gestational age, birth weight, and fHCC. Additionally, parity is included in the male WHO z-score model.

For both male and female TSF scores, the use of WHO or KEN outcomes highlighted different village effects, where KEN z-scores show Keneba has a negative effect (p=0.001) (Table C28). Gestational age has a negative relationship to male and female TSF z-scores, while parity is slightly negative for females, but slightly positive for males.

Summary: Overall, utilizing environmental, maternal, and fHCC data, models had greater predictive power for postnatal growth than prenatal growth. Maternal inputs are inconsistently significant while environmental factors (e.g. month of birth and village) and fHCC seem to have fairly strong effects on measures of infant weight and height for age z-scores. While there were no effects of categorical seasonality (e.g., wet vs. dry season of birth), there were month of birth effects.

The results of postnatal models suggest a near consistent difference in size between male infants with low fHCC and mid or high range values that presents at later ages. This difference is apparent in male weight, weight-for-height z-scores and mid-upper arm circumference at 12 months of age, and significant differences in male head circumference size at 3 and 6 months. fHCC has a negative relationship with height and weight, the effect more pronounced and significant in males.

While the model for KH length is strong, explaining 86% of variance in the study population, the models for arm measurements are among the weakest of the postnatal growth models. The only significant association identified between fHCC and female growth was a positive association with KH lengths.

Table R 2: summarizes the significant effects of all the models. In addition to the postnatal trend of low fHCC males being larger at 12months, there appears to be a negative effect of Keneba on growth.

Summary Table of Model Results						
Measure/Time	**Sex**	**Maternal Inputs**	**Environmental Factors**	**Birth Outcome**	**R^2**	**p-value (where available)**
Birth Outcome						
fHCC	Female	-	MOB: May (0.03)	Gestational age (0.001)	0.31	0.09
	Male	-	Villages: Keneba (0.04); Karantaba (0.05)	-	0.38	0.017
Gestational Age	Female	-	Village: Jali (0.013)	Birth weight (<0.0001); fHCC (0.021)	0.49	0.003
	Male	-	-	Birth weight (<0.0001)	0.36	0.01
Birth Weight	Female	Height (0.006)	-	Gestational age (<0.0001); fHCC (0.05)	0.66	0.015
	Male	-	MOB: Feb. (0.006); May (0.014); Nov. (0.04); Village: Kantong Kunda (0.007), Nyorro Jattaba (0.035)	Gestational age (<0.0001)	0.69	0.0004
Prenatal Growth - Third Trimester						
Crown-Rump	Both	SES: Mid (0.05)	MOB: Feb (0.02), May (0.0001); Village: Nyorro Jattaba (0.01)	Birth weight (<0.0001)	0.47	<0.0001
AC	Both	Lost a Child (N, 0.009); Proxy wealth (0.04); Education (0.044)	-	Birth weight (0.001)	0.21	0.0003

	Female	-	-	-	0.32	0.35
AC z-score	Male	Proxy wealth (0.02); Education (0.015);	MOB: Oct. (0.026)	-	0.2	0.057
	Female	-	-	Birth weight (0.002)	0.46	0.012
OFD	Male	Parity (0.003)	Village: Kantong Kunda (0.05), Kuli Kunda (0.01)	Birth weight (0.01)	0.5	0.13
	Female	-	-	-	0.32	0.26
OFD z-score	Male	Proxy wealth (0.007); crowding ratio (0.016)	Village: Jattaba (0.05), Kantong Kunda (0.002); Manduar (0.04); MOB: Feb (0.03); Aug. (0.04), Oct. (<0.001)	Birth weight (0.003)	0.73	0.06
BPD z-score	Both	Proxy wealth (0.01); Education (0.03)	Village: Keneba (0.03), Manduar (0.01); MOB: April (0.008), Feb. (0.005)	Birth weight (0.009)	0.38	0.04
HC	Both	-	-	Birth weight (0.0003)	0.31	0.002
HC z-score	Both	-	Village: Nyorro Jattaba (0.045); MOB: Aug. (0.04)	-	0.22	0.26
TL	Both	Parity (0.003); Crowding ratio (0.046); SES: Low (0.012)	-	-	0.26	0.048
	Female	-	Village: Manduar (0.006)	-	0.35	0.5
FL	Male	SES: Mid (0.007)	MOB: Sep. (0.03)	fHCC (0.003)	0.39	0.08
	Female	Lost a Child (N, 0.04)	Village: Joli (0.002), Kemoto (0.02)	Birth weight (0.03)	0.43	0.04
FL z-score	Male	SES: Mid (0.002)	MOB: Jan (0.01); Sept. (0.006)	fHCC (0.003)	0.42	0.03
Postnatal Growth - Birth - Twelve Months						

Weight	Female	-	MOB: Jan (0.01); Village: Kantong Kunda (0.009)	-	0.77
	Male	Parity (0.04); Crowding ratio (0.04)	Village: Kuli Kunda (0.01); Sankandi (0.007); Kantong Kunda (0.005)	fHCC (0.04)	0.75
WFA WHO z-score	Female	-	Village: Jali (0.03); Kantong Kunda (0.001)	-	0.68
	Male	Crowding ratio (0.03); Parity (0.02)	MOB: June (0.05); Village: Kuli Kunda (0.04); Kantong Kunda (0.005); Sankandi (0.003)	fHCC (0.02)	0.75
WFA KEN z-score	Female	-	Village: Jali (0.03); Kantong Kunda (0.005)	-	0.68
	Male	Crowding ratio (0.03)	Village: Kuli Kunda (0.01); Kantong Kunda (0.005); Sankandi (0.007)	fHCC (0.02)	0.75
Height	Female	-	MOB: Feb. (0.04), Aug. (0.03), Sept. (0.02); Village: Jattaba (0.001); Karantaba (0.01)	-	-0.37
	Male	SES: High (0.02)	MOB: Feb. (0.001), Sept. (0.001); Village: Joli (0.02), Keneba (0.003), Nyorro Jattaba (0.02)	-	-0.54
HFA WHO z-score	Female	SES: Low (0.02)	Village: Nyorro Jattaba (0.05)	Birth weight (0.007)	0.67
	Male	-	Village: Janneh Kunda (0.0004); MOB: Oct. (0.03); Nov. (0.01)	Birth weight (<0.0001)	0.66
HFA KEN z-score	Female	-	-	Birth weight (0.02)	0.67

	Male	-	Village: Janneh Kunda (0.002)	Birth weight (<0.0001); fHCC (0.04)	0.66
WHZ WHO z-score	Female	-	MOB: June (0.05)	-	0.57
	Male	-	Village: Nyorro Jattaba (0.05), Sankandi (0.008)	-	0.6
WHZ KEN z-score	Female	-	MOB: June (0.05)	-	0.55
	Male	-	Village: Nyorro Jattaba (0.026), Sankandi (0.03)	fHCC (0.03)	0.58
HC	Female	Education (0.005)	Village: Manduar (0.04); MOB: April (0.04)	Birth weight (0.05)	0.86
	Male	-	Village: Keeba (0.007)	Birth weight (0.001)	0.86
HC WHO z-score	Female	-	Village: Manduar (0.02), Nyorro Jattaba (0.04); MOB: April (0.03)	-	0.76
	Male	-	-	Birth weight (0.002)	0.78
HC KEN z-score	Female	-	Village: Manduar (0.01), Nyorro Jattaba (0.03); MOB: April (0.02)	-	0.71
	Male	-	-	Birth weight (0.001)	0.71
Knee Heel Length	Female	-	Village: Karantaba (0.02)	Birth weight (0.003)	0.86
	Male	-	Village: Janneh Kunda (0.02)	Birht weight (0.0002)	0.88
MUAC	Female	-	-	Birth weight (0.02)	0.52
	Male	SES: Low (0.03); Parity (0.01)	Village: Baja (0.03), Kantong Kunda (0.02); Keneba (0.002); MOB: May (0.01)	Birth weight (0.002)	0.6

MUAC WHO z-score	Female	Parity (0.04); Crowding ratio (0.04)	MOB: Nov. (0.02)	-	0.9
	Male	-	Village: Kemoto (0.03); Keneba (0.01)	Birth weight (0.04)	0.8
MUAC KEN z-score	Female	-	Village: Nyorro Jattaba (0.03); MOB: April (0.02)	Birth weight (0.001); Gestational age (0.008)	0.5
	Male	-	Village: Kemoto (0.04); Keneba (0.03)	Birth weight (0.01)	0.53
TSF	Female	-	-	Gestational age (0.004)	0.45
	Male	Parity (0.03)	Village: Keneba (0.002); Baja (0.01); MOB: May (0.01)	-	0.45
TSF WHO z-score	Female	-	-	Gestational age (0.004)	0.79
	Male	-	MOB: May (0.03)	-	0.76
TSF KEN z-score	Female	Parity (0.03)	Village: Nyorro Jattaba (0.02)	Gestational age (0.005)	0.46
	Male	-	Village: Keneba (0.01); MOB: May (0.05)	-	0.43

Discussion

The primary aims of this thesis were to determine any relationships between seasonality, maternal sociodemographic factors, and fetal hair cortisol and describe any relationships or effects that these factors had on prenatal growth, birth outcome, and postnatal growth in rural Gambian infants. Despite the significance of "month of birth" in many outcomes, these results show no significant effect of season of birth or conception on fHCC, pre- or postnatal growth, but several village effects were identified. Additionally, these results show no effect of SES on fHCCs, but it is a contributing factor in many of the growth models.

While exploratory, I also hypothesized that infants with high fHCCs would have altered postnatal growth patterns, assuming a bell curve effect, where expression either too low or too high would have a negative effect on growth. I found that fHCC has a relationship to several male growth outcomes, but not those of females. Notably, female high fHCC was predictive of later gestational age and longer knee heel lengths at birth. Specifically, results suggest that (1) males with low fHCCs are born at later gestational ages and grow better during the first year of life, (2) those with mid-range fHCCs are variably affected, and (3) those with high fHCCs are smaller in size at 12 months (**Fig. D1**). Overall, these results suggest that fHCCs are largely independent from maternal and environmental factors and that male infant growth may be more affected by higher fetal hair cortisol than females, who seem buffered from these effects.

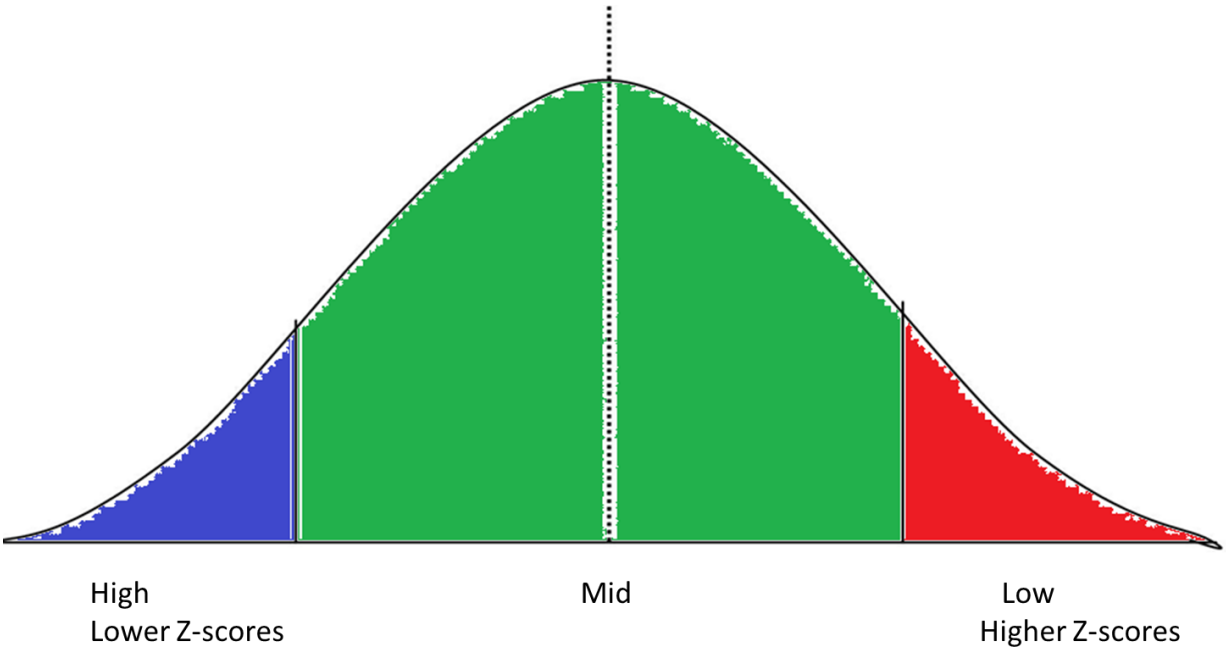

Figure D 1: These results suggest that there may be an advantage, seen in larger size and higher z-scores, for male infants with low fHCCs (red), while mid-range fHCC male infants (green) are largely unaffected, and high fHCC male infants (blue) may have compromised growth.

Fetal hair cortisol:

A primary aim of this project was to explore the relationship between environmental and maternal sociodemographic factors and fHCCs to test the hypothesis that maternal stress, via elevated levels of circulating cortisol, translates to the fetus and affects outcomes at birth and beyond. This idea follows the suggestion that maternal-fetal HPA axes dysregulation is a possible mechanism that leads to the adverse outcomes of prenatal stress (Kinsella and Monk, 2009). Studies have characterized maternal prenatal stress through surveys and/or by characterizing maternal stress through cortisol levels collected in saliva (de Weerth et al., 2003; Davis et al., 2007; Davis and Sandman, 2010; Luecken et al. 2013), blood (Glynn et al., 2007; Suglia et al., 2010; Davis et al., 2011), amniotic fluid (Sarkar et al., 2008; O'Connor et al., 2013), or hair cortisol (Hoffman et al., 2016a). These studies describe various adverse outcomes

linking maternal prenatal stress and infant health. A common outcome is infant cortisol reactivity to stress (reviewed by Fardi and Bernstein, 2016), that is the amount of cortisol that is released in response to a stressor and the time to recovery/baseline is altered and often exaggerated, suggesting that the intrauterine experience of stress alters infant cortisol expression and HPA axis activity. By examining fHCCs, it was possible to see if 'altered' activity was present during the course of pregnancy—while this is not directly reflective of a stress response in this study, the measure still reflects fetal exposure and process of cortisol during gestation. Additionally, it allowed me to determine if fHCCs reflected maternal inputs.

I was unable to consider circulating levels of maternal cortisol, however Hoffman et al. (2016a) compared maternal and fetal hair cortisol levels and found no relationship. Additionally, they performed detailed psychological assessments and collected surveys of self-reported stress and found no relationship between maternal perceived stress and fetal hair cortisol. While I considered sociodemographic factors, which can be defined independently of individual perception, I did not find fetal hair cortisol to be strongly related to SES (although education had a slight, positive relationship with male fHCC). Proxy measurements, such as calculated SES scores, education, broad assessments of living conditions such as household crowding, did not allow me to gauge perceptions of stress within the cohort, meaning I cannot definitively say that maternal stress experienced during gestation does not influence fetal cortisol exposure, at least what is captured in hair. However, the general lack of a relationship between maternal factors and stressors found in this study is in line with the findings of Hoffman et al (2016a).

The models I constructed for this study, including maternal and environmental factors, gestational age and birth weight were only able to account for ~38% of the variation in the cohorts fHCCs. This suggests that there are other mechanisms and factors, such as genetics, or

effects associated with maternal weight and gain during pregnancy, or factors that were not captured, such as diet and nutrition, influencing fHCCs. Despite the vastly different conditions (environmentally, socioeconomically, and ethnically) the average concentrations of fHCCs from the Gambian infants and those born in the Denver based study (Hoffman et al., 2016a) are comparable:

Study	Location	Neonate age at collection	Hair cortisol Average and Error (pg/mg)
Fardi et al.	West Kiang Region, Gambia	7 days	212.3 ± 92.1 Range: 23.1-641.1
Hoffman et al. 2016	Denver, CO, USA	0 days (birth)	281.8 ± 141.6 Range: unknown

This suggests that fetal hair cortisol expression may be largely driven by factors independent of environment, but that a small portion of fHCCs are responsive to maternal and environmental cues given the 38% of variation in males that was explained and the significance of the model. There may also be sex differences in sensitivity to increased fetal cortisol exposure (see postnatal discussion below).

These findings are incongruous with studies done in macaques, which are often used as models for human gestation and early infancy (Carter, 2007). Kapoor et al. (2016) found a significant decrease in hair cortisol expression in neonates whose mothers were exposed to an acute stressor during pregnancy compared to control. Grant et al. (2016) found significant correlations between maternal cortisol and newborn hair cortisol, such that a greater increase in maternal cortisol during gestation was positively associated with newborn hair cortisol concentrations. These nonhuman primate studies suggest that there may be a link, association, or translation process that ties maternal cortisol and experience of stress to fetal exposure, production, or processing of cortisol. However, this study and Hoffman et al.'s (2016 a) suggest

in humans that measures of fHCCs are not a strong reflection of maternal cortisol expression or perception of stress.

This may mean that due to variation in levels of fetal cortisol expression or differences in placental function and efficiency, fetal hair cortisol concentrations in humans may not be an ideal measure to describe fetal exposure to maternal stress or cortisol in utero. This may also be due to the fact that human infants are secondarily altricial and significant development occurs postnatally, including that of their circadian rhythms, which will later regulate HPA axis activity and cortisol expression. Human infants do not develop an independent circadian rhythm until one to three months of life (Rivkees, 2003; Ivars et al., 2015) and this is largely dependent on activity of regulatory centers in the brain (e.g. the hypothalamus). If these brain areas develop later than in the macaque brain, then there may be a difference in fetal HPA axis and cortisol activity. Recent research also suggests that the circadian rhythm is malleable into childhood and adolescence (Simons et al., 2015), but there may be a critical postnatal period between one and three months where baseline activity and rhythmicity is established (Ivars et al., 2015). This critical period of development also suggests that breast milk, which not only contains cortisol, but reflects the maternal diurnal rhythm of cortisol (van der Voorn et al., 2016), may be critical for early infant development of HPA axis rhythmicity. These critical periods of development are only recently being investigated in relation to each other, and understanding the rate of development of circadian rhythms and HPA axis activity in species used as animal models is important. For example, it is possible that primates develop this this system at earlier ages (Conley et al., 2004), while altricial rodents are with even less developmental maturity than humans, but mature more rapidly (Rivkees, 2003; Rivkees, 2007).

Prenatal Growth:

Despite hypothesizing that prenatal growth would relate to fetal cortisol expression, there was little evidence to suggest that prenatal growth and fHCC expression are correlated. Fetal cortisol plays a significant role in organ maturation in the third trimester and is crucial for preparation for extra-uterine life to make sure the infant is prepared to metabolize resources and breathe independently from the mother and placenta (Liggins, 1994). In the present data set, fetal hair cortisol is more strongly correlated with measures of postnatal growth. Fetal hair cortisol is not expected to reflect the total amount of cortisol in circulation (free plus bound cortisol), as free cortisol is what is most deposited in hair (Cone, 1996; Villain et al., 2003; Anielski, 2008).

Given the apparent independence of fetal hair cortisol expression from maternal and environmental factors, it may be that the placenta and its enzymatic barrier (via 11β-HSD2), and the placenta's own production of cortisol, buffer or are buffered from the developing fetus. Understanding the mechanisms that drive fetal cortisol expression, the way the fetus process and, potentially stores, endogenous and exogenous (here, meaning the hormones produced by the mother) cortisol is crucial to understanding intrauterine fetal cortisol expression and its importance, especially as the free cortisol captured in fetal hair cortisol may not reflect the extra-uterine environment as researchers hoped. Fetal hair cortisol may only represent the fetus' production and processing of the hormone while maternal cortisol is buffered, processed differently by the fetus, or acts on different systems without necessarily being free cortisol available for the fetus to deposit in hair.

Additionally, growth rate should be a consideration in future studies. While I did run preliminary analyses, using growth rate as an outcome, these data were largely incomplete for prenatal measures, requiring measures across multiple time points. For postnatal growth data,

rate did not yield any significant models or relationships. However, it remains as an area of future research as the body does not grow at uniform rates pre- or postnatally. For example, male head circumference and abdominal circumference scores tend to be greater in the second trimester than those of females, however male femur length measures are smaller compared female fetuses (Broere-Brown et al., 2016). Postnatally, head circumference grows at sex-specific rates where male head circumference grows more slowly. However, in general, males tend to grow more rapidly during the first 12 months of age. There after females tend to have higher body weights as well (Broere-Brown et al., 2016). Future studies should consider growth rate, especially as a component that contributes to male sensitivity, and especially as this sensitivity may begin in utero. A faster growth rate likely correlates with an increase energy demand and there may be greater consequences or impact on growth if this occurs in a resource-harsh environment.

Postnatal Outcomes:

fHCCs and birth weight have a slight, negative correlation. The correlation between fHCCs and gestational age is sex-dependent. For females, gestational age and fHCCs show a positive relationship, where female infants with high levels of fHCCs were born at later gestational ages. However, males with low fHCCs were born at significantly later gestational ages compared to male infants with high fHCCs. In other words, male and female fHCCs show inverse relationships with gestational age. This difference may suggest that the relationship between fHCC and male growth and male sensitivity could begin in utero.

In all, this is consistent with findings that suggest that males have a tendency to be more sensitive to environmental and prenatal stress (Trivers and Willard, 1973; Wells, 2000;

Kirchengast and Hartmann, 2009) and the idea of the male newborn disadvantage (Stinson, 1985; Stevenson et al., 2000). Evolutionary studies predict an excess of males at the time of conception (Lowry, 1979; Cagnacci et al., 2003), but due to male susceptibility to morbidity and increased mortality rate, there are equal, if not fewer males at 5 years of age (Corsini and Viazzo, 1997). Studies of the starvation and harsh conditions at Leningrad (1941-1944) show that, while both males and females are impacted, low birth weights and morbidities occurred at greater rates in male infants (Antonov, 1947). However, evidence from The Dutch Hunger Winter (1944-1945) does not show a significant sex difference in birth weights (Susser, 1981). Interestingly, there is evidence that more males are conceived during favorable conditions than females, which may indicate a selection pressure that supports that females may be better equipped to handle harsher conditions during early life (Cagnacci et al., 2003).

In general, rates of male infant mortality tend to be greater than that of females; if there are strong preferences for a male offspring within a culture, this can vary (Stinson, 1985; Fledderjohann et al., 2014). This trend holds true in Gambia as well (UNICEF, 2015).

While restricted to animal models, several more recent studies have shown that male rats have a certain susceptibility to prenatal stress and that the alterations that occur can be long term. These epigenetic modifications include changes in methylation of genes associated with CRH and glucocorticoid receptor expression (Mueller and Bale, 2008). Additionally, early pregnancy stress was found to cause increases in the following proteins: PPARα, IGFBP-1, HIF3α, and GLUT4 in male, but not female, placentas. The changes that led to this increased expression could have long-term consequences for growth by impacting metabolic function and insulin sensitivity.

A recent study based in Gambia also supports that males and females have different patterns of growth, based on their epigenetic makeup at birth (Khulan et al., 2012). While this study focused on micronutrient supplementation during the periconceptional period, their control group consisted of infants whose mothers who were not given supplements and showed that males and females, under suboptimal maternal nutrient status, showed different developmental trajectories. They also found that a greater number of gene loci underwent differential methylation in males than in females, suggesting that they are more impacted than females in the early postnatal period. The primary genes that were affected in males were involved in fatty acid uptake, transport and metabolism, liver function, cholesterol metabolism, and vitamin A synthesis (Khulan et al., 2012). The influences on fatty acid uptake and metabolism (Innis, 2014; Vlaardingerbroek et al., 2014; Fleddermann et al., 2014) and vitamin A (Cetin et al., 2010; Gernand et al., 2016) have implications on growth success for male infants. What relationship fetal cortisol has to these epigenetic modifications, be they causal or correlative, remains unknown, but should be an area of future research.

My data showed no effect of season of conception or birth on outcomes. While birth months were often significant factors in modeling growth outcomes, there was no pattern of 'wet' or 'dry' months and may suggest that the effects were due to more immediately local causes such as resources for an individual, or within a family, or village. Keneba, while one of the larger villages and the nearest to the Medical Research Counicl (MRC) clinic, had one of the more consistent negative effects on pre- and postnatal growth outcomes for males. Interestingly, male infants in Keneba had higher fHCCs than in other villages. While living in Keneba allows easy access to the MRC clinic, it is also possible that increased means and access may exacerbate the consequence of socioeconomic disparity, creating social tension and stress. Additionally, it

may lead to increased postnatal use of breastmilk substitutes, such as formula and the early introduction of weaning foods; as it is few mothers in Gambia exclusively breastfeed at six months, as WHO recommends; in fact, a recent study of 28 villages shows that 67% were partially breastfed given breastmilk and complementary foods before this time (Eriksen et al., 2016). Interestingly, Eriksen et al. (2016) found that rates of exclusive breastfeeding until six months of age are lowest in four villages nearest the MRC clinic: Jali, Kantong Kunda, Keneba, and Manduar. The rate of exclusive breastfeeding in these villages was 12% lower than those in surrounding villages (Eriksen et al., 2016). The premature introduction of weaning foods could alter growth patterns (Agostoni et al., 1999; Kavian et al., 2015) and may lead to suboptimal growth, especially when paired with prenatal stress and risk of low nutrition during gestation and early life.

In this study, there is a near-consistent negative effect associated with Keneba, where male infants in the village do not grow as well as male infants in other villages. Additionally, there are negative effects of Kantong Kunda and Manduar on male postnatal growth. Jali was noted for its negative effect on female gestational age and weight-for-age z-scores. While these effects are not consistently noted in prenatal growth, the same four villages noted by Eriksen et al. have occasional negative influences on prenatal growth infants regardless of sex. It is possible that there is an interaction between the premature introduction of weaning foods and male infants with high fHCCs that ultimately impacts growth. There may also be an effect due to being in proximity to the MRC clinic, such as a more extreme distribution of wealth and therefore social perception of inequity, or an assumption of health that comes with increased theoretical access, or an unknown interaction that is interacting with growth and fHCC expression. It’s important to

note that there were uneven sample sizes and that this is possible contributing to the appearance of these effects, but remains a possible factor and area of future study.

While SES has been used in other studies as a form of prenatal stress, citing limitations on resources and/or access (Bradley et al., 1997; Romo et al., 2009; Fisher et al., 2012, see introduction for further review), it did not appear to have a strong influence in fHCCs or growth outcomes. The results of this thesis show differential effects of low SES status: positive on female height for age z-scores, but negative on male weight for height z-scores and MUAC measurements and female skin fold measures. The effects were not pronounced and often inconsistent. One of the primary challenges of studying stress is defining it, as its causes vary from individual to individual. Dual approaches are often taken: self-reporting and standardized measures (e.g. socioeconomics). Standardized measures, however, neglect individual perception and experience of stress. Even if SES was not an ideal measure of stress, these results remain consistent with the results from Hoffman et al. (2016a) study who found that fHCCs were independent of SES and maternal perception of stress.

It should also be noted that cortisol has an inhibitory effect on cell growth. Studies of cancer cells have shown that cortisol has an inhibitory effect on the synthesis of insulin-like growth factor-binding protein-1 (IGFBP-1, McCarthy et al., 1990) and IGFBP-5 in bone cell cultures (Gabbitas et al., 1996). The growth stunting effect of cortisol has been thoroughly explored in fish, namely salmon and trout (reviewed by Pickering, 1993), and growth stunting and disrupted stress responses have been observed in children (Fernald and Grantham-McGregor, 1997; Dobrova-Krol et al., 2008). Hormones involved in the HPA axis have direct impacts on growth hormones and the related regulatory pathways. Specifically, CRH inhibits growth hormone (GH), thyroid releasing hormone (TRH), thyroid stimulating hormone (TSH)

while cortisol and other glucocorticoids have multiple roles, including the direct inhibition of GH and TSH secretion which could have severe consequences for growth (Tsigos and Chrousos, 2002). If dysregulation occurs at an early age, or if the baseline of HPA axis function is established in utero, there could be long-term consequences on growth and hormone regulation.

Overall, these results indicate fetal hair cortisol may have a fetal programming effect particularly in males, influencing growth outcomes that emerge at one year of life. Fetal cortisol seems to be differentially sensitive to maternal and environmental effects, but largely driven by fetal physiology and development, rather than influenced by maternal experience. Males are more sensitive to increased fetal cortisol and show altered growth patterns depending on their concentration of cortisol in the first neonatal week. Future research is needed to understand the mechanisms, causal and correlative relationships to identify determinants of fHCCs and to clarify the relationship and significance of fetal cortisol to infant growth.

Future Areas of Study:

Currently, it appears that fHCCs are determined by factors largely independent of maternal factors. This is a potential credit to the protection provided by the placenta and uterine environment, but also highlights how little is known about the mechanisms active in translating maternal and external stress to the fetus and the significance of fetal cortisol in development and infant growth. To begin understanding these mechanisms and human variation, information on the baseline expression of cortisol during pregnancy, across race/ethnicities is needed, along with more characterization on fetal cortisol and fetal hair growth as this only the second study of its kind, and the first to look at fHCCs and growth. This project shows that there is a differential impact of fHCCs on female and male growth; this suggests a sensitivity and fetal programming

effect in males. This does not mean that females are immune, but rather the consequences may present in different ways.

Studies of rodent models have shown that, in response to various stressors, female rats showed heightened responsiveness, neurological changes, and altered HPA axis compared to male offspring (McCormick et al., 1995; Weinstock, 2007; Mueller and Bale, 2007). Female fetuses have also demonstrated decreased 11β-HSD2 enzyme activity when compared to males in response to different maternal health conditions (e.g. asthma, reviewed by O'donnell 2009). A study of male guinea pigs demonstrated that, in response to maternal stress, male offspring show altered growth and reduced body weight (Kapoor and Matthews, 2005). Primate models suggest that a relationship between maternal experience of stress (Kapoor et al., 2016) and maternal cortisol expression correlates with fHCCs exists (Grant et al., 2016). Taken together, these studies suggest a complicated picture, where sexes may respond differently, and with different sensitivity, depending on the stressor and species.

Ultimately, the involved mechanisms are still largely speculated on and deserve significant future research. The pathway between maternal HPA axis activity and fetal experience of stress may not be direct. The enzymatic placental barrier, 11β-HSD2, converts cortisol to the inactive form cortisone. What role cortisone plays or the consequence of exposure is mostly unknown, but it's suggested that cortisol is converted to cortisone which then helps maintain fetal tissue (Murphy, 1981). Not only is the role of cortisone in the fetus unexplored, understanding if variation in fetal hair cortisol expression is the result of altered 11β-HSD2 activity would clarify the relationship between maternal and fetal cortisol expression. It may be possible that the fetus is still being exposed to maternal cortisol, but this exposure is due to placental inefficiency in processing cortisol. It is also possible that there are glucocorticoid-

induced epigenetic changes that impact fetal development and infant growth, leading to the many consequences often associated with stress, but these act independently from fetal HPA axis activity and cortisol expression. Moreover, the infant is not with an entrained HPA axis circadian rhythm. This suggests that, while fetal HPA axis activity and cortisol expression may develop in response to the intrauterine and early life environment, it remains a largely plastic system. It may be shaped by epigenetic changes to glucocorticoid receptor expression (Mueller and Bale, 2008), or it is possible that maternal stress acts on genes indirectly related to HPA axis activity (Khulan et al., 2012), but ones that can still impact growth and development. As a part of characterizing and understanding the impact of stimuli during this critical period of development, breast milk, the cortisol in it, and the interaction between breastfeeding, circadian rhythm and HPA axis development should be an area of future research. These potential mechanisms could exacerbate the consequences of negative stimulus during fetal development.

Another layer that needs to be explored in conjunction with hormonal mechanisms and their significance for fetal and infant development are the epigenetic changes that can occur in the mother in response to stress and trauma, which can lead to intergenerational or transgenerational effects of prenatal stress (Reviewed in Bowers and Yehuda, 2016). Studies of survivors from war-torn regions, such as the Tutsi of Rwanda (Perroud et al., 2014) and mothers surviving in eastern Democratic Republic of Congo (Rodney and Mulligan, 2014; Kertes et al., 2016), show significant genome-wide epigenetic changes, many that are similar between the mother and infant. These studies show that women who have experienced repeated traumas have epigenetic modifications, often in *NRC*-related genes (glucocorticoid receptor, and other steroid hormones) (Perroud et al., 2014; Rodney and Mulligan, 2014; Kertes et al., 2016) and those for CRH (Kertes et al., 2016). These maternal epigenetic modifications, which are abnormal when

compared to non-stressed counterparts, manifest in their children. In The Gambia, the harsh seasonality and potential for intra-household competition (Wittrup, 1990, Adewuya et al., 2007; Bove and Valeggia, 2009), desire for support (Bove and Valeggia, 2009; Sawyer et al., 2011), and the significant pressure of childrearing (Beldsoe, 1994; Bledsoe et al., 1998; Hough 2010) could create an environment of chronic, repeated undernourishment and vulnerability. Any resulting epigenetic changes, especially those that lead to changes in glucocorticoid receptor expression could interact with sensitivity to cortisol, making the impact of elevated exposure *in utero* more significant to infant development. Identification of such epigenetic modifications should be included in future research in The Gambia. Moreover, the differences and similarities between acute and chronic, or intergenerational, stress need to be better characterized to shed light on the adaptive relevance of these outcomes and modifications and to better understand the roles of the different mechanisms involved. For example, do acute stressors elicit the same epigenetic changes as the chronic/extreme stressors, or are those modifications occurring in response to different stimuli? Perhaps only hormonal modifications and alteration of the HPA axis occur in response to an acute stressor, while intergenerational stress triggers an epigenetic modification that would impact not only the first generation born, but the second.

Conclusion

This study shows that fHCCs influence male, but not female infant growth in rural Gambia. Differences in female and male fHCCs and the relationship to gestational age, and later growth, may indicate that these effects may be the result of fetal programming, specifically in males. These results support of Well's (2012) argument that the responsiveness of the developing fetus, and male sensitivity, are likely reflective of a harsh, unpredictable past environment, rather than one of the perceived future as the predictive adaptive response suggests (Gluckman et al., 2005). That males, and not females, are affected provides support for Well's argument as male chances of survival are lower in the first year of life. Males with low fetal hair cortisol may have an advantage, growing better during the first year of life, while those with mid-range fetal hair cortisol are largely unaffected, and male infants with high fHCCs are smaller. This reduction in growth may reflect an adaptive mechanism to slow growth during a critical, vulnerable period, even if it may result in increased risk of later life diseases. Follow up study on these infants to determine if they have increased susceptibility to morbidities and infections during the first year of life would be useful to see if they have any immune compromises or more immediate consequences besides smaller body measurements.

Moreover, it still cannot be said that females are not impacted by fHCCs. Studies of animal models would suggest that males may experience increased deficits in growth, where females may be initially protected, but present with altered HPA axis and endocrine function later in life, increasing susceptibility to depression and mood disorders. The timing of effects and the long-term impact, and the influence on neurological and behavioral development require interdisciplinary-based study and long-term observation to begin to understand. Ultimately, these results show that fetal hair cortisol is driven by factors primarily independent from maternal

experience, but that high levels of fetal hair cortisol may be involved in or indicate a fetal programming effect that has long-term, negative consequences on male growth.

References

Abiodun, O. A., Adetoro, O. O., & Ogunbode, O. O. (1993). Psychiatric morbidity in a pregnant population in Nigeria. General Hospital Psychiatry, 15(2), 125–128.

Abrams, S. A. (2007). In utero physiology: role in nutrient delivery and fetal development for calcium, phosphorus, and vitamin D. The American Journal of Clinical Nutrition, 85(2), 604S–607S.

Accorsi, Pier A., Elena Carloni, Paola Valsecchi, Roberta Viggiani, Matteo Gamberoni, Carlo Tamanini, and Eraldo Seren. "Cortisol determination in hair and faeces from domestic cats and dogs." General and Comparative Endocrinology 155, no. 2 (2008): 398-402.

Adair, L. S., & Prentice, A. M. (2004). A critical evaluation of the fetal origins hypothesis and its implications for developing countries. The Journal of Nutrition, 134(1), 191–193.

Aderibigbe, Y. A., Gureje, O., & Omigbodun, O. (1993). Postnatal emotional disorders in Nigerian women. A study of antecedents and associations. The British Journal of Psychiatry, 163(5), 645–650.

Adewuya, A. O., Ola, B. A., Aloba, O. O., Dada, A. O., & Fasoto, O. O. (2007a). Prevalence and correlates of depression in late pregnancy among Nigerian women. Depression and Anxiety, 24(1), 15–21.

Adewuya, A. O., Ola, B. A., Aloba, O. O., Dada, A. O., & Fasoto, O. O. (2007b). Prevalence and correlates of depression in late pregnancy among Nigerian women. Depression and Anxiety, 24(1), 15–21.

Agostoni, C., Grandi, F., Gianni, M. L., Silano, M., Torcoletti, M., Giovannini, M., & Riva, E. (1999). Growth patterns of breast fed and formula fed infants in the first 12 months of life: an Italian study. Archives of Disease in Childhood, 81(5), 395–399.

Agyemang, Kwaku. (2005). Trypantolerant livestock in the context of trypanosomaiasis intervention strategies. PAAT Information Service Publications (A FAO report).

Ahiara M, Ida I, Yuuki N, Oshima A, Kumano H, Takahashi K, Fukuda M, Oriuchi N, Endo K, Matsudda H, Mikuni M. 2007. HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic. Psychiatric Research: Neuroimagining. 155: 245-256.

Akresh, R., Chen, J. J., & Moore, C. (2010). Altruism, cooperation and intrahousehold allocation: agricultural production in polygynous households. mimeo, University of Illinois, Urbana-Champaign.

Akresh, R., Chen, J. J., & Moore, C. T. (2012). Productive Efficiency and the Scope for Cooperation in Polygynous Households. American Journal of Agricultural Economics, 94(2), 395–401.

Alam, D., van Raaij, J., Hautvast, J., Yunus, M., & Fuchs, G. (2003). Energy stress during pregnancy and lactation: consequences for maternal nutrition in rural Bangladesh. European Journal of Clinical Nutrition, 57, 151–156.

Anielski, P. "Hair analysis of anabolic steroids in connection with doping control—results from horse samples." Journal of mass spectrometry 43, no. 7 (2008): 1001-1008.

Antonov, A. N. (1947). Children born during the siege of Leningrad in 1942. The Journal of pediatrics, 30(3), 250-259.

Anya, S. E. (2004). Seasonal variation in the risk and causes of maternal death in the Gambia: malaria appears to be an important factor. The American Journal of Tropical Medicine and Hygiene, 70(5), 510–513.

Appleton, A. A., Armstrong, D. A., Lesseur, C., Lee, J., Padbury, J. F., Lester, B. M., & Marsit, C. J. (2013). Patterning in Placental 11-B Hydroxysteroid Dehydrogenase Methylation According to Prenatal Socioeconomic Adversity. PLoS ONE, 8(9), e74691.

Badyaev, A.V., Uller, T. (2009). Parental effects in ecology and evolution: mechanisms, processes and implications. Philosophical Transactions of the Royal Society B: Biological Sciences. 364, 1169–1177.

Bailey, M. T., Lubach, G. R., & Coe, C. L. (2004). Prenatal stress alters bacterial colonization of the gut in infant monkeys. Journal of Pediatric Gastroenterology and Nutrition, 38(4), 414–421.

Bale, T. L. (2011). Sex differences in prenatal epigenetic programing of stress pathways. Stress, 14(4), 348–356.

Bale, T. L., & Vale, W. W. (2004). CRF and CRF receptors: role in stress responsivity and other behaviors. Annu. Rev. Pharmacol. Toxicol., 44, 525-557.

Barker, D., Godfrey, K.M., Gluckmand, P.D., Harding, J.E., Owens, J.A., Robinson, J.S. (1993). Fetal nutrition and cardivascular disease in adult life. The Lancet. 341, 938–941.

Barker, D., Osmond, C. (1986). Infant mortality, childhood nutrition, and ischaemic heard disease in England and Wales. Stroke. 431, 0–54.

Barker, D.J., Osmond, C., Winter, P.D., Margetts, B., Simmonds, S.J. (1989). Weight in infancy and death from ischemic heart disease. The Lancet. 334, 577–580.

Barrell, R. A. E., & Rowland, M. G. M. (1979). Infant foods as a potential source of diarrhoeal illness in rural West Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene, 73(1), 85–91.

Bartholomew, D. J., & Bartholomew, D. J. (1967). Stochastic models for social processes. Wiley London. Retrieved from http://tocs.ulb.tu-darmstadt.de/46113037.pdf

Baschat, D. A. A. (2004). Fetal responses to placental insufficiency: an update. BJOG: An International Journal of Obstetrics & Gynaecology, 111(10), 1031–1041.

Bates, C. J., P. H. Bates, M. Dardenne, A. Prentice, P. G. Lunn, C. A. Northrop-Clewes, S. Hoare et al. "A trial of zinc supplementation in young rural Gambian children." British Journal of Nutrition 69, no. 01 (1993): 243-255.

Benediktsson, R., Calder, A. A., Edwards, C. R., & Seckl, J. R. (1997). Placental 11β-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. Clinical endocrinology, 46(2), 161-166.

Bergman, K., Sarkar, P., Glover, V., & O'Connor, T. G. (2010). Maternal Prenatal Cortisol and Infant Cognitive Development: Moderation by Infant–Mother Attachment. Biological Psychiatry, 67(11), 1026–1032.

Bertram, C. E., & Hanson, M. A. (2002). Prenatal programming of postnatal endocrine responses by glucocorticoids. Reproduction, 124(4), 459-467.

Bertram, C., A. R. Trowern, N. Copin, A. A. Jackson, and C. B. Whorwood. "The Maternal Diet during Pregnancy Programs Altered Expression of the Glucocorticoid Receptor and Type 2 11β-Hydroxysteroid Dehydrogenase: Potential Molecular Mechanisms Underlying the Programming of Hypertension in Utero 1." Endocrinology 142, no. 7 (2001): 2841-2853.

Bicego, G. T., & Boerma, J. T. (1996). Maternal Education and Child Survival: A Comparative Study of Survey Data from 17 Countries. Social Science and Medicine, 36(1), 207–28.

Bispham, J., Gopalakrishnan, G. S., Dandrea, J., Wilson, V., Budge, H., Keisler, D. H., … Symonds, M. E. (2003). Maternal Endocrine Adaptation throughout Pregnancy to Nutritional Manipulation: Consequences for Maternal Plasma Leptin and Cortisol and the Programming of Fetal Adipose Tissue Development. Endocrinology, 144(8), 3575–3585.

Bledsoe, C. (1994). “Children are like young bamboo trees”: Potentiality and reproduction in Sub-Saharan Africa. New York, New York: Oxford University Press.

Bledsoe, C., Banja, F., & Hill, A. G. (1998). Reproductive Mishaps and Western Contraception: An African Challenge to Fertility Theory. Population and Development Review, 24(1), 15.

Bogin, B., Silva, M. I. V., & Rios, L. (2007). Life history trade-offs in human growth: Adaptation or pathology?. American Journal of Human Biology, 19(5), 631-642.

Boivin, J., Bunting, L., Collins, J. A., & Nygren, K. G. (2007). International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Human Reproduction, 22(6), 1506–1512.

Börzsönyi, B., Demendi, C., Pajor, A., Rigó, J., Marosi, K., Ágota, A., … Joó, J. G. (2012). Gene expression patterns of the 11β-hydroxysteroid dehydrogenase 2 enzyme in human placenta from intrauterine growth restriction: the role of impaired feto-maternal glucocorticoid metabolism. European Journal of Obstetrics & Gynecology and Reproductive Biology, 161(1), 12–17.

Bouvette-Turcot, A.A., 2016. Maternal history of early adversity and child emotional development: investigating intervening factors.

Bouvette-Turcot, A.-A., Unternaehrer, E., Gaudreau, H., Lydon, J. E., Steiner, M., & Meaney, M. J. (2017). The joint contribution of maternal history of early adversity and adulthood depression to socioeconomic status and potential relevance for offspring development. Journal of Affective Disorders, 207, 26–31.

Bove, R., & Valeggia, C. (2009). Polygyny and women’s health in sub-Saharan Africa. Social Science & Medicine, 68(1), 21–29.

Bowers, M. E., & Yehuda, R. (2016). Intergenerational transmission of stress in humans. Neuropsychopharmacology, 41(1), 232-244.

Bradley, Robert H., Leanne Whiteside-Mansell, Judith A. Brisby, and Bettye M. Caldwell. "Parents' socioemotional investment in children." Journal of Marriage and the Family (1997): 77-90.

Braveman, P. A., Heck, K., Egerter, S., Marchi, K. S., Dominguez, T. P., Cubbin, C., … Curtis, M. (2015). The role of socioeconomic factors in black–white disparities in preterm birth. American Journal of Public Health, 105(4), 694–702.

Broere-Brown, Z. A., Baan, E., Schalekamp-Timmermans, S., Verburg, B. O., Jaddoe, V. W., & Steegers, E. A. (2016). Sex-specific differences in fetal and infant growth patterns: a prospective population-based cohort study. Biology of Sex Differences, 7(1), 65.

Brown, Alan S., Ezra S. Susser, Shang P. Lin, Richard Neugebauer, and Jack M. Gorman. "Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944-45." The British Journal of Psychiatry 166, no. 5 (1995): 601-606.

Buitelaar, J. K., Huizink, A. C., Mulder, E. J., de Medina, P. G. R., & Visser, G. H. A. (2003). Prenatal stress and cognitive development and temperament in infants. Neurobiology of Aging, 24, S53–S60.

Bussières, E.-L., Tarabulsy, G. M., Pearson, J., Tessier, R., Forest, J.-C., & Giguère, Y. (2015). Maternal prenatal stress and infant birth weight and gestational age: A meta-analysis of prospective studies. Developmental Review, 36, 179–199.

Cagnacci, A. (2003). The male disadvantage and the seasonal rhythm of sex ratio at the time of conception. Human Reproduction, 18(4), 885–887.

Campbell, D. I., Elia, M., & Lunn, P. G. (2003). Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation. The Journal of Nutrition, 133(5), 1332–1338.

Canivet, C., Östergren, P.-O., Rosén, A.-S., Jakobsson, I., & Hagander, B. (2005). Infantile colic and the role of trait anxiety during pregnancy in relation to psychosocial and socioeconomic factors. Scandinavian Journal of Public Health, 33(1), 26–34.

Carter, Anthony Michael. "Animal models of human placentation–a review." Placenta 28 (2007): S41-S47.

Castillo-Duran, C., & Weisstaub, G. (2003). Zinc supplementation and growth of the fetus and low birth weight infant. The Journal of Nutrition, 133(5), 1494S–1497S.

Ceesay, S. M., Prentice, A. M., Cole, T. J., Foord, F., Poskitt, E. M., Weaver, L. T., & Whitehead, R. G. (1997). Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. Bmj, 315(7111), 786–790.

Cetin, I., Berti, C., & Calabrese, S. (2010). Role of micronutrients in the periconceptional period. Human Reproduction Update, 16(1), 80–95.

Christian, P. (2003). Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. BMJ, 326(7389), 571–571.

Christian, P. (2010). Micronutrients, Birth Weight, and Survival. Annual Review of Nutrition, 30(1), 83–104.

Christian, P., & Stewart, C. P. (2010). Maternal Micronutrient Deficiency, Fetal Development, and the Risk of Chronic Disease. Journal of Nutrition, 140(3), 437–445.

Chrousos, G. P. (2009). Stress and disorders of the stress system. Nature Reviews Endocrinology, 5(7), 374-381.

Chrousos, George P., and Tomoshige Kino. "Glucocorticoid action networks and complex psychiatric and/or somatic disorders." Stress 10, no. 2 (2007): 213-219.

Cianfarani, S., Germani, D., Rossi, L., Argiro, G., Boemi, S., Lemon, M., … Branca, F. (1998). IGF-I and IGF-binding protein-1 are related to cortisol in human cord blood. European Journal of Endocrinology, 138(5), 524–529.

Cohen, Sheldon. "Psychosocial models of the role of social support in the etiology of physical disease." Health psychology 7, no. 3 (1988): 269.

Cole, T. J., & Parkin, J. M. (1977). The growth of young children: A comparison of The Gambia and Uganda. Transactions of the Royal Society of Tropical Medicine and Hygiene, 71(3), 196–199.

Coleman, R., Morison, L., Paine, K., Powell, R. A., & Walraven, G. (2006). Women's reproductive health and depression: A community survey in the Gambia, West Africa. Social Psychiatry and Psychiatric Epidemiology, 41(9), 720–727.

Collins, J. W., David, R. J., Symons, R., Handler, A., Wall, S. N., & Dwyer, L. (1999). Low-income African American mother's perception of exposure to racial descrimination and infant birth weight: an exploratory study. Pediatric Research, 45.

Collinson, A., Moore, S. E., Cole, T. J., & Prentice, A. M. (2003). Birth season and environmental influences on patterns of thymic growth in rural Gambian infants. Acta Paediatrica, 92(9), 1014–1020.

Cone, Edward J. "Mechanisms of drug incorporation into hair." Therapeutic drug monitoring 18, no. 4 (1996): 438-443.

Conley, A. J., Pattison, J. C., & Bird, I. M. (2004, November). Variations in adrenal androgen production among (nonhuman) primates. In Seminars in reproductive medicine (Vol. 22, No. 04, pp. 311-326). Copyright© 2004 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

Corsini, C.A. and Viazzo, P.P. eds. (1997). The Decline of Infant and Child Mortality/Gender mortality differences from birth to puberty in Italy, 1887–1940. UNICEF. Printed in the Netherlands. 73-93.

Cox, John L., Jeni M. Holden, and Ruth Sagovsky. "Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale." The British journal of psychiatry 150, no. 6 (1987): 782-786.

Crofton, P. M. (2004). Cortisol and growth hormone responses to spontaneous hypoglycaemia in infants and children. Archives of Disease in Childhood, 89(5), 472–478.

D'Anna-Hernandez, K. L., Ross, R. G., Natvig, C. L., & Laudenslager, M. L. (2011). Hair cortisol levels as a retrospective marker of hypothalamic–pituitary axis activity throughout pregnancy: Comparison to salivary cortisol. Physiology & Behavior, 104(2), 348–353.

Dauphin, A. (2013). The Role of Polygyny in the Intra-Household Efficiency of Agricultural Production in West Africa.

Davenport, Matthew D., Stefan Tiefenbacher, Corrine K. Lutz, Melinda A. Novak, and Jerrold S. Meyer. "AnalysiLius of endogenous cortisol concentrations in the hair of rhesus macaques." General and comparative endocrinology 147, no. 3 (2006): 255-261.

Davis, E. P., & Sandman, C. A. (2010). The Timing of Prenatal Exposure to Maternal Cortisol and Psychosocial Stress Is Associated With Human Infant Cognitive Development. Child Development, 81(1), 131–148.

Davis, E. P., & Sandman, C. A. (2012). Prenatal psychobiological predictors of anxiety risk in preadolescent children. Psychoneuroendocrinology, 37(8), 1224–1233.

Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicz-Demet, A., & Sandman, C. A. (2007). Prenatal Exposure to Maternal Depression and Cortisol Influences Infant Temperament. Journal of the American Academy of Child & Adolescent Psychiatry, 46(6), 737–746.

de Onis, M., Garza, C., Victora, C. G., Onyango, A. W., Frongillo, E. A., & Martines, J. (2004). The WHO Multicentre Growth Reference Study: planning, study design, and methodology. Food and nutrition bulletin, 25(1 suppl1), S15-S26.

de Weerth, C., Zijl, R. H., & Buitelaar, J. K. (2003). Development of cortisol circadian rhythm in infancy. Early human development, 73(1), 39-52.

De-Regil, L. M., Fernández-Gaxiola, A. C., Dowswell, T., & Peña-Rosas, J. P. (2010). Effects and safety of periconceptional folate supplementation for preventing birth defects. The Cochrane Library.

Dibba, Bakary, Ann Prentice, Mustapha Ceesay, Dorothy M. Stirling, Tim J. Cole, and Elizabeth ME Poskitt. "Effect of calcium supplementation on bone mineral accretion in Gambian children accustomed to a low-calcium diet." The American journal of clinical nutrition 71, no. 2 (2000): 544-549.

Dobrova-Krol, N. A., van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Cyr, C., & Juffer, F. (2008). Physical growth delays and stress dysregulation in stunted and non-stunted Ukrainian institution-reared children. Infant Behavior and Development, 31(3), 539–553.

Dominguez-Salas, P., Moore, S. E., Baker, M. S., Bergen, A. W., Cox, S. E., Dyer, R. A., … Hennig, B. J. (2014). Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nature Communications, 5.

Eccles, M. P., T. J. Cole, and R. G. Whitehead. "Identification of factors affecting infant growth in developing countries." Archives of disease in childhood 64, no. 11 (1989): 1559-1565.

Entringer, S., Buss, C., & Wadhwa, P. D. (2010). Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. Current Opinion in Endocrinology, Diabetes, and Obesity, 17(6), 507.

Erhuma, A., Salter, A. M., Sculley, D. V., Langley-Evans, S. C., & Bennett, A. J. (2007). Prenatal exposure to a low-protein diet programs disordered regulation of lipid metabolism in the aging rat. American Journal of Physiology-Endocrinology and Metabolism, 292(6), E1702-E1714.

Erhuma, Aml, Andrew M. Salter, Dean V. Sculley, Simon C. Langley-Evans, and Andrew J. Bennett. "Prenatal exposure to a low-protein diet programs disordered regulation of lipid metabolism in the aging rat." American Journal of Physiology-Endocrinology and Metabolism 292, no. 6 (2007): E1702-E1714.

Eriksen, Kamilla G., Johnson William, Darboe Momodou K., Bah Amat, Moore, Soophie E. (2016). Benefits and determinants of exclusive breastfeeding in a rural West African Setting: Data from the ENID trial. Abstracts from the 18th International Society for Research in Human Milk and Lactation Conference. Breastfeeding Medicine. 11(2): A49-50.

Eyles, D., Burne, T., & McGrath, J. (2011). Vitamin D in fetal brain development. Seminars in Cell & Developmental Biology, 22(6), 629–636.

Faisal-Cury, A., Menezes, P., Araya, R., & Zugaib, M. (2009). Common mental disorders during pregnancy: prevalence and associated factors among low-income women in São Paulo, Brazil: Depression and Anxiety during Pregnancy. Archives of Women's Mental Health, 12(5), 335–343.

Fardi, S. A., & Bernstein, R. M. "Maternal environment, prenatal stress, and offspring cortisol reactivity: A meta-analysis." American Journal of Physical Anthropology, vol. 159: 141-142. March 2016.

Fernald, L.C. and Grantham-McGregor, S.M. (1998). Stress response in school-age children who have been growth retarded since early childhood. The American journal of clinical nutrition, 68(3), 691-698.

Fernald, Lia CH, and Megan R. Gunnar. "Poverty-alleviation program participation and salivary cortisol in very low-income children." Social science & medicine 68.12 (2009): 2180-2189.

Fisher, J., Cabral de Mello, M., Patel, V., Rahman, A., Tran, T., Holton, S., & Holmes, W. (2012). Prevalence and determinants of common perinatal mental disorders in women in low- and lower-middle-income countries: a systematic review. Bulletin of the World Health Organization, 90(2), 139–149H.

Fisher, Jane, Meena Cabral de Mello, Vikram Patel, Atif Rahman, Thach Tran, Sara Holton, and Wendy Holmes. "Prevalence and determinants of common perinatal mental disorders in women in low-and lower-middle-income countries: a systematic review." Bulletin of the World Health Organization 90, no. 2 (2012): 139-149.

Fledderjohann, J., Agrawal, S., Vellakkal, S., Basu, S., Campbell, O., Doyle, P., ... & Stuckler, D. (2014). Do girls have a nutritional disadvantage compared with boys? Statistical Models of breastfeeding and food consumption inequalities among Indian Siblings. PloS one, 9(9), e107172.

Fledderjohann, J., Agrawal, S., Vellakkal, S., Basu, S., Campbell, O., Doyle, P., … Stuckler, D. (2014). Do Girls Have a Nutritional Disadvantage Compared with Boys? Statistical Models of Breastfeeding and Food Consumption Inequalities among Indian Siblings. PLoS ONE, 9(9), e107172.

Fleddermann, M., Demmelmair, H., Grote, V., Nikolic, T., Trisic, B., & Koletzko, B. (2014). Infant formula composition affects energetic efficiency for growth: The BeMIM study, a randomized controlled trial. Clinical Nutrition, 33(4), 588–595.

Fourie, Nicolaas H., and Robin M. Bernstein. "Hair cortisol levels track phylogenetic and age related differences in hypothalamic–pituitary–adrenal (HPA) axis activity in non-human primates." General and comparative endocrinology 174, no. 2 (2011): 150-155.

Frankel, S., Elwood, P., Smith, G. D., Sweetnam, P., & Yarnell, J. (1996). Birthweight, body-mass index in middle age, and incident coronary heart disease. The Lancet, 348(9040), 1478-1480.

Fulford, A. J., Rayco-Solon, P., & Prentice, A. M. (2006). Statistical modelling of the seasonality of preterm delivery and intrauterine growth restriction in rural Gambia. Paediatric and Perinatal Epidemiology, 20(3), 251–259.

Gabbitas, B., Pash, J. M., Delany, A. M., & Canalis, E. (1996). Cortisol inhibits the synthesis of insulin-like growth factor-binding protein-5 in bone cell cultures by transcriptional mechanisms. Journal of Biological Chemistry, 271(15), 9033–9038.

Gale, C. R., Robinson, S. M., Harvey, N. C., Javaid, M. K., Jiang, B., Martyn, C. N., … Cooper, C. (2008). Maternal vitamin D status during pregnancy and child outcomes. European Journal of Clinical Nutrition, 62(1), 68–77.

Gali Ramamoorthy, T., Begum, G., Harno, E., & White, A. (2015). Developmental programming of hypothalamic neuronal circuits: impact on energy balance control. Frontiers in neuroscience, 9, 126.

Gambia. (2012). World Health Organization.

Gareri, Joey, and Gideon Koren. "Prenatal hair development: implications for drug exposure determination." Forensic science international 196, no. 1 (2010): 27-31.

Gausia, K., Fisher, C., Ali, M., & Oosthuizen, J. (2009). Antenatal depression and suicidal ideation among rural Bangladeshi women: a community-based study. Archives of Women's Mental Health, 12(5), 351–358.

Gernand, A. D., Schulze, K. J., Stewart, C. P., West, K. P., & Christian, P. (2016). Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nature Reviews Endocrinology, 12(5), 274–289.

Gillman, M. W., Smith, G. D., Hanson, M. A., & Spencer, H. G. (2009). Developmental Origins of Health and Disease Across Generations–Theory, Observation, Experiment. In Early Life Origins of Human Health and Disease (pp. 52-64). Karger Publishers.

Gitau, Rachel, Alan Cameron, Nicholas M. Fisk, and Vivette Glover. "Fetal exposure to maternal cortisol." The Lancet 352, no. 9129 (1998): 707-708.

Gleixner, Andreas, and Heinrich HD Meyer. "Detection of estradiol and testosterone in hair of cattle by HPL/EIA." Fresenius' journal of analytical chemistry 357, no. 8 (1997): 1198-1201.

Glover, Vivette, Kristin Bergman, Pampa Sarkar, and Thomas G. O'Connor. "Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety." Psychoneuroendocrinology 34, no. 3 (2009): 430-435.

Glover, Vivette. "Annual research review: prenatal stress and the origins of psychopathology: an evolutionary perspective." Journal of Child Psychology and Psychiatry 52, no. 4 (2011): 356-367.

Gluckman, P. D., & Hanson, M. A. (2004). Developmental origins of disease paradigm: a mechanistic and evolutionary perspective. Pediatric research, 56(3), 311-317.

Gluckman, P. D., Hanson, M. A., & Spencer, H. G. (2005). Predictive adaptive responses and human evolution. Trends in ecology & evolution, 20(10), 527-533.

Glynn, L. M., Schetter, C. D., Chicz-DeMet, A., Hobel, C. J., & Sandman, C. A. (2007). Ethnic differences in adrenocorticotropic hormone, cortisol and corticotropin-releasing hormone during pregnancy. Peptides, 28(6), 1155–1161.

Glynn, L. M., Schetter, C. D., Chicz-DeMet, A., Hobel, C. J., & Sandman, C. A. (2007). Ethnic differences in adrenocorticotropic hormone, cortisol and corticotropin-releasing hormone during pregnancy. Peptides, 28(6), 1155–1161.

Godfrey, K. M., & Barker, D. J. (2001). Fetal programming and adult health. Public health nutrition, 4(2b), 611-624.

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. The Lancet, 371(9606), 75–84.

Grant, K. S., Worlein, J. M., Meyer, J. S., Novak, M. A., Kroeker, R., Rosenberg, K., … Burbacher, T. M. (2016). A longitudinal study of hair cortisol concentrations in Macaca nemestrina mothers and infants. American Journal of Primatology.

Greenwood, B. M., Bradley, A. K., Greenwood, A. M., Byass, P., Jammeh, K., Marsh, K., … Hayes, R. (1987). Mortality and morbidity from malaria among children in a rural area of The Gambia, West Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene, 81(3), 478–486.

Gunnar, Megan R., Kristin Frenn, Sandi S. Wewerka, and Mark J. Van Ryzin. "Moderate versus severe early life stress: Associations with stress reactivity and regulation in 10–12-year-old children." Psychoneuroendocrinology 34, no. 1 (2009): 62-75.

Gutteling, B. M., Weerth, C. de, & Buitelaar, J. K. (2005). Prenatal stress and children's cortisol reaction to the first day of school. Psychoneuroendocrinology, 30(6), 541–549.

Hajat, Anjum, Ana Diez-Roux, Tracy G. Franklin, Teresa Seeman, Sandi Shrager, Nalini Ranjit, Cecilia Castro, Karol Watson, Brisa Sanchez, and Clemens Kirschbaum. "Socioeconomic and race/ethnic differences in daily salivary cortisol profiles: the multi-ethnic study of atherosclerosis." Psychoneuroendocrinology 35, no. 6 (2010): 932-943.

Hanington, Lucy, Paul Ramchandani, and Alan Stein. "Parental depression and child temperament: Assessing child to parent effects in a longitudinal population study." Infant Behavior and Development 33, no. 1 (2010): 88-95.

Hanlon, C., Medhin, G., Alem, A., Tesfaye, F., Lakew, Z., Worku, B., … Prince, M. (2009). Impact of antenatal common mental disorders upon perinatal outcomes in Ethiopia: the P-MaMiE population-based cohort study. Tropical Medicine & International Health, 14(2), 156–166.

Hargraves, J. L., & Hadley, J. (2003). The contribution of insurance coverage and community resources to reducing racial/ethnic disparities in access to care. Health services research, 38(3), 809-829.

Harpham, T. (1996). Urban health in The Gambia: a review. Health & Place, 2(1), 45–49.

Hart, P. H., Lucas, R. M., Walsh, J. P., Zosky, G. R., Whitehouse, A. J. O., Zhu, K., … Mountain, J. A. (2015). Vitamin D in Fetal Development: Findings From a Birth Cohort Study. PEDIATRICS, 135(1), e167–e173.

Harvey, Paul H., and Timothy H. Clutton-Brock. (1985). "Life history variation in primates." Evolution. 559-581.

Hauser, J., Dettling-Artho, A., Pilloud, S., Maier, C., Knapman, A., Feldon, J., & Pryce, C. R. (2007). Effects of Prenatal Dexamethasone Treatment on Postnatal Physical, Endocrine, and Social Development in the Common Marmoset Monkey. Endocrinology, 148(4), 1813–1822.

Hawkesworth, Sophie, Celia G. Walker, Yankuba Sawo, Anthony JC Fulford, Landing MA Jarjou, Gail R. Goldberg, Ann Prentice, Andrew M. Prentice, and Sophie E. Moore. "Nutritional supplementation during pregnancy and offspring cardiovascular disease risk in The Gambia." The American journal of clinical nutrition 94, no. 6 Suppl (2011): 1853S-1860S.

Heckmann, M., Hartmann, M. F., Kampschulte, B., Gack, H., Bödeker, R.-H., Gortner, L., & Wudy, S. A. (2005). Cortisol Production Rates in Preterm Infants in Relation to Growth and Illness: A Noninvasive Prospective Study Using Gas Chromatography-Mass Spectrometry. The Journal of Clinical Endocrinology & Metabolism, 90(10), 5737–5742.

Heijmans, Bastiaan T., Elmar W. Tobi, Aryeh D. Stein, Hein Putter, Gerard J. Blauw, Ezra S. Susser, P. Eline Slagboom, and L. H. Lumey. "Persistent epigenetic differences associated with prenatal exposure to famine in humans." Proceedings of the National Academy of Sciences 105, no. 44 (2008): 17046-17049.

Heim, Christine, Ulrike Ehlert, and Dirk H. Hellhammer. "The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders." Psychoneuroendocrinology 25, no. 1 (2000): 1-35.

Hill, A. G., Walraven, G., & Ratcliffe, A. A. (2000). Separate lives, different interests: male and female reproduction in Gambia.

Hobel, C., & Culhane, J. (2003). Role of psychosocial and nutritional stress on poor pregnancy outcome. The Journal of Nutrition, 133(5), 1709S–1717S.

Hoffman, M. C., D'Anna-Hernandez, K., Benitez, P., Ross, R. G., & Laudenslager, M. L. (2016). Cortisol during human fetal life: Characterization of a method for processing small quantities of newborn hair from 26 to 42 weeks gestation. Developmental Psychobiology.

Hoffman, M. C., Mazzoni, S. E., Wagner, B. D., Laudenslager, M. L., & Ross, R. G. (2016). Measures of Maternal Stress and Mood in Relation to Preterm Birth: Obstetrics & Gynecology, 127(3), 545–552.

Holbrook, Karen A., and George F. Odland. "Structure of the human fetal hair canal and initial hair eruption." Journal of Investigative Dermatology 71, no. 6 (1978): 385-390.

Hough, C. A. (2010). Loss in childbearing among Gambia's kanyalengs: Using a stratified reproduction framework to expand the scope of sexual and reproductive health. Social Science & Medicine, 71(10), 1757–1763.

Innis, S. M. (2014). Impact of maternal diet on human milk composition and neurological development of infants. American Journal of Clinical Nutrition, 99(3), 734S–741S.

Ivars, Katrin, Nina Nelson, Annette Theodorsson, Elvar Theodorsson, Jakob O. Ström, and Evalotte Mörelius. "Development of salivary cortisol circadian rhythm and reference intervals in full-term infants." PloS one 10, no. 6 (2015): e0129502.

Jaffar, S., A. Leach, A. M. Greenwood, A. Jepson, O. Muller, M. O. C. Ota, K. Bojang, S. Obaro, and B. M. Greenwood. "Changes in the pattern of infant and childhood mortality in upper river division, The Gambia, from 1989 to 1993." Tropical Medicine & International Health 2, no. 1 (1997): 28-37.

Jaffar, S., Leach, A., Greenwood, A. M., Jepson, A., Muller, O., Ota, M. O. C., … Greenwood, B. M. (1997). Changes in the pattern of infant and childhood mortality in upper river division, The Gambia, from 1989 to 1993. Tropical Medicine & International Health, 2(1), 28–37.

Jain, V., & Singhal, A. (2012). Catch up growth in low birth weight infants: Striking a healthy balance. Reviews in Endocrine and Metabolic Disorders, 13(2), 141–147.

Jansen, J., Beijers, R., Riksen-Walraven, M., & de Weerth, C. (2010). Cortisol reactivity in young infants. Psychoneuroendocrinology, 35(3), 329-338.

Jarjou, Landing MA, Ann Prentice, Yankuba Sawo, M. Ann Laskey, Janet Bennett, Gail R. Goldberg, and Tim J. Cole. "Randomized, placebo-controlled, calcium supplementation study in pregnant Gambian women: effects on breast-milk calcium concentrations and infant birth weight, growth, and bone mineral accretion in the first year of life." The American journal of clinical nutrition 83, no. 3 (2006): 657-666.

Jarjou, Landing MA, M. Ann Laskey, Yankuba Sawo, Gail R. Goldberg, Timothy J. Cole, and Ann Prentice. "Effect of calcium supplementation in pregnancy on maternal bone outcomes in women with a low calcium intake." The American journal of clinical nutrition (2010): ajcn-29217.

Jawara, M., Pinder, M., Drakeley, C. J., Nwakanma, D. C., Jallow, E., Bogh, C., … Conway, D. J. (2008). Dry season ecology of Anopheles gambiae complex mosquitoes in The Gambia. Malaria Journal, 7(1), 156.

Jensen Peña, C., Monk, C., & Champagne, F. A. (2012). Epigenetic Effects of Prenatal Stress on 11β-Hydroxysteroid Dehydrogenase-2 in the Placenta and Fetal Brain. PLoS ONE, 7(6), e39791.

Jensen, E. C., Gallaher, B. W., Breier, B. H., & Harding, J. E. (2002). The effect of a chronic maternal cortisol infusion on the late-gestation fetal sheep. Journal of Endocrinology, 174(1), 27–36.

Jesse, D. E., Seaver, W., & Wallace, D. C. (2003). Maternal psychosocial risks predict preterm birth in a group of women from Appalachia. Midwifery, 19(3), 191–202.

Jiménez-Chillarón, J. C., Díaz, R., Martínez, D., Pentinat, T., Ramón-Krauel, M., Ribó, S., & Plösch, T. (2012). The role of nutrition on epigenetic modifications and their implications on health. Biochimie, 94(11), 2242–2263.

Johnson, William, Momodou K. Darboe, Fatou Sosseh, Patrick Nshe, Andrew M. Prentice, and Sophie E. Moore. "Association of prenatal lipid-based nutritional supplementation with fetal growth in rural Gambia." Maternal & child nutrition (2016).

Johnson, William, Seham AA Elmrayed, Andrew M. Prentice, and Sophie E. Moore. "Pre-Pregnancy Energy Balance, Gestational Weight Gain, and Small-for-Gestational Age in Rural Gambia: the Early Nutrition and Immune Development Trial (ISRCTN49285450)." The FASEB Journal 30, no. 1 Supplement (2016): 432-7.

Kajantie, E., Dunkel, L., Turpeinen, U., Stenman, U.-H., Wood, P. J., Nuutila, M., & Andersson, S. (2003). Placental 11β-Hydroxysteroid Dehydrogenase-2 and Fetal Cortisol/Cortisone Shuttle in Small Preterm Infants. The Journal of Clinical Endocrinology & Metabolism, 88(1), 493–500.

Kammerer, M., Adams, D., Von Castelberg, B., & Glover, V. (2002). Pregnant women become insensitive to cold stress. BMC pregnancy and childbirth, 2(1), 8.

Kammerer, M., Taylor, A., & Glover, V. (2006). The HPA axis and perinatal depression: a hypothesis. Archives of women's mental health, 9(4), 187-196.

Kapoor, A., Dunn, E., Kostaki, A., Andrews, M. H., & Matthews, S. G. (2006). Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids: Fetal programming of HPA function. The Journal of Physiology, 572(1), 31–44.

Kapoor, A., Lubach, G. R., Ziegler, T. E., & Coe, C. L. (2016). Hormone levels in neonatal hair reflect prior maternal stress exposure during pregnancy. Psychoneuroendocrinology, 66, 111–117.

Kapoor, A., Lubach, G., Hedman, C., Ziegler, T. E., & Coe, C. L. (2014). Hormones in infant rhesus monkeys' (Macaca mulatta) hair at birth provide a window into the fetal environment. Pediatric Research, 75(4), 476–481.

Karlen, J., Ludvigsson, J., Hedmark, M., Faresjo, A., Theodorsson, E., & Faresjo, T. (2015). Early Psychosocial Exposures, Hair Cortisol Levels, and Disease Risk. Pediatrics, 135(6), e1450–e1457.

Karmaliani, Rozina, Carla M. Bann, Mohammad A. Mahmood, Hillary S. Harris, Saeed Akhtar, Robert L. Goldenberg, and Nancy Moss. "Measuring antenatal depression and anxiety: findings from a community-based study of women in Hyderabad, Pakistan." Women & health 44, no. 3 (2007): 79-103.

Kavian, F., Scott, J., Perry, R., Byrne, R., & Magarey, A. (2015). Assessing dietary intake and growth of infants. Matern. Paediatr. Nutr. J, 1, 101.

Keenan, K., Gunthorpe, D., & Young, D. (2002). Patterns of cortisol reactivity in African-American neonates from low-income environments. Developmental Psychobiology, 41(3), 265–276.

Kent, A., Hughes, P., Ormerod, L., Jones, G., & Thilaganathan, B. (2002). Uterine artery resistance and anxiety in the second trimester of pregnancy. Ultrasound in Obstetrics and Gynecology, 19(2), 177-179.

Kertes, D. A., Kamin, H. S., Hughes, D. A., Rodney, N. C., Bhatt, S., & Mulligan, C. J. (2016). Prenatal maternal stress predicts methylation of genes regulating the hypothalamic–pituitary–adrenocortical system in mothers and newborns in the Democratic Republic of Congo. Child development, 87(1), 61-72.

Khulan, B., Cooper, W. N., Skinner, B. M., Bauer, J., Owens, S., Prentice, A. M., … Affara, N. A. (2012). Periconceptional maternal micronutrient supplementation is associated with widespread gender related changes in the epigenome: a study of a unique resource in the Gambia. Human Molecular Genetics, 21(9), 2086–2101.

King, J. C. (2006). Maternal Obesity, Metabolism, and Pregnancy Outcomes. Annual Review of Nutrition, 26(1), 271–291.

Kinsella, M. T., & Monk, C. (2009). Impact of maternal stress, depression & anxiety on fetal neurobehavioral development. Clinical obstetrics and gynecology, 52(3), 425.

Kirchengast, S., & Hartmann, B. (2009). The male disadvantage hypothesis reconsidered: is there really a weaker sex? An analysis of gender differences in newborn somatometrics and vital parameters. J Life Sci, 1(1), 63–71.

Kirschbaum, C., Tietze, A., Skoluda, N., & Dettenborn, L. (2009). Hair as a retrospective calendar of cortisol production—Increased cortisol incorporation into hair in the third trimester of pregnancy. Psychoneuroendocrinology, 34(1), 32–37.

Knutsson, Anders. "Health disorders of shift workers." Occupational medicine 53, no. 2 (2003): 103-108.

Kramer, M. S., Seguin, L., Lydon, J., & Goulet, L. (2000). Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatric and Perinatal Epidemiology, 14(3), 194–210.

Langley-Evans, S. C., G. J. Phillips, R. Benediktsson, D. S. Gardner, C. R. W. Edwards, A. A. Jackson, and J. R. Seckl. "Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat." Placenta 17, no. 2 (1996): 169-172.

Larsson, H. J., Eaton, W. W., Madsen, K. M., Vestergaard, M., Olesen, A. V., Agerbo, E., … Mortensen, P. B. (2005). Risk Factors for Autism: Perinatal Factors, Parental Psychiatric History, and Socioeconomic Status. American Journal of Epidemiology, 161(10), 916–925.

Lassi, Z. S., Salam, R. A., Haider, B. A., & Bhutta, Z. A. (2013). Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. The Cochrane Library.

Lawrence, M., Lawrence, F., Coward, W. A., Cole, T. J., & Whitehead, R. G. (1987). Energy Requirements of Pregnancy in The Gambia. The Lancet.

Lee, Phyllis C., Patricia Majluf, and Iain J. Gordon. (1991). "Growth, weaning and maternal investment from a comparative perspective." Journal of Zoology. 225(1), 99-114.

Leffelaar, E. R., Vrijkotte, T. G. M., & van Eijsden, M. (2010). Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. British Journal of Nutrition, 104(1), 108–117.

Li, M., Sloboda, D. M., & Vickers, M. H. (2011). Maternal obesity and developmental programming of metabolic disorders in offspring: evidence from animal models. Experimental diabetes research, 2011.

Liggins, G. (1994). The role of cortisol in preparing the fetus for birth. Reproduction Fertility and Development, 6(2), 141–152.

Liu, X., F. Chen, D. Guo, X. Song, and Y. Zhong. "Early pregnancy diagnosis in dairy cows based on hair progesterone analysis." Int. J. Anim. Sci 3 (1988): 123-127.

Lobel, M., Dunkel-Schetter, C., & Scrimshaw, S. C. (1992). Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychology, 11(1), 32.

Lowry, JT. (1979). Fetal mortality and sex ratio. Science. 206(4425), 4425-4428

Lucassen, P. J., Naninck, E. F. G., van Goudoever, J. B., Fitzsimons, C., Joels, M., & Korosi, A. (2013). Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics. Trends in Neurosciences, 36(11), 621–631.

Luecken, L. J., Lin, B., Coburn, S. S., MacKinnon, D. P., Gonzales, N. A., & Crnic, K. A. (2013). Prenatal stress, partner support, and infant cortisol reactivity in low-income Mexican American families. Psychoneuroendocrinology, 38(12), 3092–3101.

Lumey, L. H., and Aryeh D. Stein. "Offspring birth weights after maternal intrauterine undernutrition: a comparison within sibships." American Journal of Epidemiology 146, no. 10 (1997): 810-819.

Lunn, Peter G. "The impact of infection and nutrition on gut function and growth in childhood." Proceedings of the Nutrition Society 59, no. 01 (2000): 147-154.

Mabey, D. C., Ogbaselassie, G., Robertson, J. N., Heckels, J. E., & Ward, M. E. (1985). Tubal infertility in the Gambia: chlamydial and gonococcal serology in women with tubal occlusion compared with pregnant controls. Bulletin of the World Health Organization, 63(6), 1107.

Macbeth, B. J., M. R. L. Cattet, G. B. Stenhouse, M. L. Gibeau, and D. M. Janz. "Hair cortisol concentration as a noninvasive measure of long-term stress in free-ranging grizzly bears (Ursus arctos): considerations with implications for other wildlife." Canadian Journal of Zoology 88, no. 10 (2010): 935-949.

Madhavan, S., & Bledsoe, C. H. (2001). The compound as a locus of fertility management: The case of The Gambia. Culture, Health & Sexuality, 3(4), 451–468.

Mahon, P., Harvey, N., Crozier, S., Inskip, H., Robinson, S., Arden, N., … Godfrey, K. (2010). Low maternal vitamin D status and fetal bone development: Cohort study. Journal of Bone and Mineral Research, 25(1), 14–19.

Marques, A. H., Bjørke-Monsen, A.-L., Teixeira, A. L., & Silverman, M. N. (2015). Maternal stress, nutrition and physical activity: Impact on immune function, CNS development and psychopathology. Brain Research, 1617, 28–46.

Marques, A. H., O'Connor, T. G., Roth, C., Susser, E., & Bjørke-Monsen, A.-L. (2013). The influence of maternal prenatal and early childhood nutrition and maternal prenatal stress on offspring immune system development and neurodevelopmental disorders. Frontiers in Neuroscience, 7.

Martin, A., Connelly, A., Bland, R. M., & Reilly, J. J. (2016). Health impact of catch-up growth in low-birth weight infants: systematic review, evidence appraisal, and meta-analysis: Health impact of catch-up growth. Maternal & Child Nutrition.

McCarthy, T.L., Centrella M., and Canalis, E. (1990). Cortisol inhibits the synthesis of insulin-like growth factor-I in skeletal cells. Endocrinology, 126(3), 1569-1575.

McCauley, M. E., van den Broek, N., Dou, L., & Othman, M. (2015). Vitamin A supplementation during pregnancy for maternal and newborn outcomes. The Cochrane Library.

McCormick, C. M., Smythe, J. W., Sharma, S., & Meaney, M. J. (1995). Sex-specific effects of prenatal stress on hypothalamic-pituitary-adrenal responses to stress and brain glucocorticoid receptor density in adult rats. Developmental Brain Research, 84(1), 55-61.

McGregor, Ian A., and Dean A. Smith. "A health, nutrition and parasitological survey in a rural village (Keneba) in west Kiang, Gambia." Transactions of the Royal Society of Tropical Medicine and Hygiene 46, no. 4 (1952): 403-427.

Meise, K., von Engelhardt, N., Forcada, J., & Hoffman, J. I. (2016). Offspring Hormones Reflect the Maternal Prenatal Social Environment: Potential for Foetal Programming? PLOS ONE, 11(1), e0145352.

Meyer, J., Novak, M., Hamel, A., & Rosenberg, K. (2014). Extraction and Analysis of Cortisol from Human and Monkey Hair. Journal of Visualized Experiments, (83).

Miles, K., Shaw, M., Paine, K., Hart, G. J., & Ceesay, S. (2001). Sexual health seeking behaviours of young people in the Gambia. Journal of Adolescence, 24(6), 753–764.

Mirabzadeh, A., Dolatian, M., Forouzan, A. S., Sajjadi, H., Majd, H. A., & Mahmoodi, Z. (2013). Path Analysis Associations Between Perceived Social Support, Stressful Life Events and Other Psychosocial Risk Factors During Pregnancy and Preterm Delivery. Iranian Red Crescent Medical Journal, 15(6), 507–514.

Montagna, William, and Richard A. Ellis, eds. The biology of hair growth. Elsevier, 2013.

Moore, S. E. (2004). Comparative analysis of patterns of survival by season of birth in rural Bangladeshi and Gambian populations. International Journal of Epidemiology, 33(1), 137–143.

Moore, S. E., Cole, T. J., Poskitt, E. M., Sonoko, B., Whitehead, R. G., McGregor, I. A., & Prentice, A. M. (1997). Season of birth predicts mortality in rural Gambia. Nature, 388, 23–25.

Moore, S. E., Collinson, A. C., & Prentice, A. M. (2001). Immune function in rural Gambian children is not related to season of birth, birth size, or maternal supplementation status. The American Journal of Clinical Nutrition, 74(6), 840–847.

Moore, Sophie E. "Early life nutritional programming of health and disease in The Gambia." Journal of developmental origins of health and disease 7, no. 02 (2016): 123-131.

Moore, Sophie E., Anthony JC Fulford, Momodou K. Darboe, Modou Lamin Jobarteh, Landing M. Jarjou, and Andrew M. Prentice. "A randomized trial to investigate the effects of pre-natal and infant nutritional supplementation on infant immune development in rural Gambia: the ENID trial: Early Nutrition and Immune Development." BMC pregnancy and childbirth 12, no. 1 (2012): 107.

Mueller, Bridget R., and Tracy L. Bale. "Sex-specific programming of offspring emotionality after stress early in pregnancy." Journal of Neuroscience 28, no. 36 (2008): 9055-9065.

Mulligan, C., D'Errico, N., Stees, J., & Hughes, D. (2012). Methylation changes at NR3C1 in newborns associate with maternal prenatal stress exposure and newborn birth weight. Epigenetics, 7(8), 853–857.

Murphy, B. E. (1981). Ontogeny of cortisol-cortisone interconversion in human tissue: fetal development. Journal of Steroid Biochemistry, 14, 881–817.

Murphy, V. E., Smith, R., Giles, W. B., & Clifton, V. L. (2006). Endocrine Regulation of Human Fetal Growth: The Role of the Mother, Placenta, and Fetus. Endocrine Reviews, 27(2), 141–169.

Mustoe, A. C., Birnie, A. K., Korgan, A. C., Santo, J. B., & French, J. A. (2012). Natural variation in gestational cortisol is associated with patterns of growth in marmoset monkeys (Callithrix geoffroyi). General and Comparative Endocrinology, 175(3), 519–526.

Nyanzi, S. (2007). Empowering traditional birth attendants in The Gambia: A local strategy to redress issues of access, equity and sustainability. CODESRIA.

Nyanzi, S., Manneh, H., & Walraven, G. (2007). Traditional Birth Attendants in Rural Gambia: Beyond Health to Social Cohesion. African Journal of Reproductive Health, 11(1), 43.

O'Donnell, K. J., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T. G., & Glover, V. (2012). Maternal prenatal anxiety and downregulation of placental 11β-HSD2. Psychoneuroendocrinology, 37(6), 818–826.

O'connor, T. G., Bergman, K., Sarkar, P., & Glover, V. (2013). Prenatal cortisol exposure predicts infant cortisol response to acute stress. Developmental psychobiology, 55(2), 145-155.

Ota, E., Mori, R., Middleton, P., Tobe-Gai, R., Mahomed, K., Miyazaki, C., & Bhutta, Z. A. (2015). Zinc supplementation for improving pregnancy and infant outcome. The Cochrane Library.

Owolabi, O., Marong, L., Muhammad, A., Townend, J., Idoko, O., & Ota, M. (2015). Seasonal changes in birth weight in a semi urban community in the Gambia: A 4 year retrospective study and lessons for the future. Austin Journal of Public Health and Epidemiology, 2(1), 1–6.

Paine, K., Hart, G., Jawo, M., Ceesay, S., Jallow, M., Morison, L., … Shaw, M. (2002). "Before we were sleeping, now we are awake": Preliminary evaluation of the Stepping Stones sexual health programme in The Gambia. African Journal of AIDS Research, 1(1), 39–50.

Pariante, Carmine M., and Andrew H. Miller. "Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment." Biological psychiatry 49, no. 5 (2001): 391-404.

Patel, V., Rahman, A., Jacob, K. S., & Hughes, M. (2004). Effect of maternal mental health on infant growth in low income countries: new evidence from South Asia. Bmj, 328(7443), 820–823.

Peacock, J. L., Bland, J. M., & Anderson, H. R. (1995). Preterm delivery: effects of socioeconomic factors, psychological stress, smoking, alcohol, and caffeine. Bmj, 311(7004), 531–535.

Peña, C. J., Monk, C., & Champagne, F. A. (2012). Epigenetic effects of prenatal stress on 11β-hydroxysteroid dehydrogenase-2 in the placenta and fetal brain. PloS one, 7(6), e39791.

Penev, P. D., Kolker, D. E., Zee, P. C., & Turek, F. W. (1998). Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease. The American journal of physiology, 275(6 Pt 2), H2334-7.

Perroud, N., Rutembesa, E., Paoloni-Giacobino, A., Mutabaruka, J., Mutesa, L., Stenz, L., ... & Karege, F. (2014). The Tutsi genocide and transgenerational transmission of maternal stress: epigenetics and biology of the HPA axis. The World Journal of Biological Psychiatry, 15(4), 334-345.

Petraglia, F., Hatch, M. C., Lapinski, R., Stomati, M., Reis, F. M., Cobellis, L., & Berkowitz, G. S. (2001). Lack of effect of psychosocial stress on maternal corticotropin-releasing factor and catecholamine levels at 28 weeks' gestation. Journal of the Society for Gynecologic Investigation, 8(2), 83-88.

Pezük, Pınar, Jennifer A. Mohawk, Laura A. Wang, and Michael Menaker. "Glucocorticoids as entraining signals for peripheral circadian oscillators." Endocrinology 153, no. 10 (2012): 4775-4783.

Pickering, A. (1991). Stress and Fish Production. Aquaculture, 111, 51–63.

Pike, I. L. (2005). Maternal stress and fetal responses: Evolutionary perspectives on preterm delivery. American Journal of Human Biology, 17(1), 55–65.

Poskitt, E. M. E., T. J. Cole, and R. G. Whitehead. "Less diarrhoea but no change in growth: 15 years' data from three Gambian villages." Archives of Disease in Childhood 80, no. 2 (1999): 115-120.

Potts, R. (1998). Variability selection in hominid evolution. Evolutionary Anthropology: Issues, News, and Reviews, 7(3), 81-96.

Prentice, A. M., & Goldberg, G. R. (2000). Energy adaptations in human pregnancy: limits and long-term consequences. The American Journal of Clinical Nutrition, 71(5), 1226s–1232s.

Prentice, A. M., & Moore, S. E. (2005). Early programming of adult diseases in resource poor countries. Archives of Disease in Childhood, 90(4), 429–432.

Prentice, A. M., & Prentice, A. (1988). Reproduction against the Odds: Women in Gambia eat too little and work too hard but still have babies. New Scientist, 42–46.

Prentice, A., Prentice, A. M., Cole, T. J., & Whitehead, R. G. (1983). Determinants of variations in breast milk protective factor concentrations of rural Gambian mothers. Archives of Disease in Childhood, 58, 518–522.

Prentice, Andrew M., and Alison A. Paul. "Fat and energy needs of children in developing countries." The American journal of clinical nutrition 72, no. 5 (2000): 1253s-1265s.

Prentice, Andrew M., Yery A. Mendoza, Dora Pereira, Carla Cerami, Rita Wegmuller, Anne Constable, and Jörg Spieldenner. "Dietary strategies for improving iron status: balancing safety and efficacy." Nutrition reviews 75, no. 1 (2017): 49-60.

Prentice, Ann, M. Ann Laskey, Jacquie Shaw, Geoffrey J. Hudson, Kenneth C. Day, Landing MA Jarjou, Bakary Dibba, and Alison A. Paul. "The calcium and phosphorus intakes of rural Gambian women during pregnancy and lactation." British Journal of Nutrition 69, no. 03 (1993): 885-896.

Rahman et al. 2001. Can maternal depression increase infant risk of illness and growth impairment in developing countries.pdf. (n.d.).

Rahman, A., Bunn, J., Lovel, H., & Creed, F. (2007). Association between antenatal depression and low birthweight in a developing country. Acta Psychiatrica Scandinavica, 115(6), 481–486.

Rahman, A., Harrington, R., & Bunn, J. (2002). Can maternal depression increase infant risk of illness and growth impairment in developing countries? Child: Care, Health and Development, 28(1), 51–56.

Rahman, A., Iqbal, Z., & Harrington, R. (2003). Life events, social support and depression in childbirth: perspectives from a rural community in the developing world. Psychological Medicine, 33(7), 1161–1167.

Ratcliffe, A. A., Hill, A. G., Harrington, D. P., & Walraven, G. (2002). Reporting of fertility events by men and women in rural Gambia. Demography, 39(3), 573–586.

Rayco-Solon, P., Fulford, A. J., & Prentice, A. M. (2005). Differential effects of seasonality on preterm birth and intrauterine growth restriction in rural Africans. The American Journal of Clinical Nutrition, 81(1), 134–139.

Reeb, K. G., Graham, A. V., Zyzanski, S. J., & Kitson, G. C. (1987). Predicting low birthweight and complicated labor in urban black women: a biopsychosocial perspective. Social Science & Medicine, 25(12), 1321–1327.

Renaville, R., Hammadi, M., & Portetelle, D. (2002a). Role of the somatotropic axis in the mammalian metabolism. Domestic Animal Endocrinology, 23(1), 351–360.

Renaville, R., Hammadi, M., & Portetelle, D. (2002b). Role of the somatotropic axis in the mammalian metabolism. Domestic Animal Endocrinology, 23(1), 351–360.

Rich-Edwards, J. W., Stampfer, M. J., Manson, J. E., Rosner, B., Hankinson, S. E., Colditz, G. A., ... & Willet, W. C. (1997). Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. Bmj, 315(7105), 396-400.

Rickard, I. J., & Lummaa, V. (2007). The predictive adaptive response and metabolic syndrome: challenges for the hypothesis. Trends in Endocrinology & Metabolism, 18(3), 94-99.

Rickard, I. J., Courtiol, A., Prentice, A. M., Fulford, A. J. C., Clutton-Brock, T. H., & Lummaa, V. (2012). Intergenerational effects of maternal birth season on offspring size in rural Gambia. Proceedings of the Royal Society B: Biological Sciences, 279(1745), 4253–4262.

Rini, C. K., Dunkel-Schetter, C., Wadhwa, P. D., & Sandman, C. A. (1999). Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychology, 18(4), 333.

Rippe, R. C. A., Noppe, G., Windhorst, D. A., Tiemeier, H., van Rossum, E. F. C., Jaddoe, V. W. V., … van den Akker, E. L. T. (2016). Splitting hair for cortisol? Associations of socio-economic status, ethnicity, hair color, gender and other child characteristics with hair cortisol and cortisone. Psychoneuroendocrinology, 66, 56–64.

Rivkees, S. A. (2003). Developing circadian rhythmicity in infants. Pediatrics, 112(2), 373–381.

Rivkees, S. A. (2007). The development of circadian rhythms: from animals to humans. Sleep medicine clinics, 2(3), 331-341.

Roberts, S. B., Paul, A. A., Cole, T. J., & Whitehead, R. G. (1982). Seasonal changes in activity, birth weight and lactational performance in rural Gambian women. Transactions of the Royal Society of Tropical Medicine and Hygiene, 76(5), 668–678.

Robinette, W. L., Gashwiler, J. S., Low, J. B., & Jones, D. A. (1957). Differential Mortality by Sex and Age among Mule Deer. The Journal of Wildlife Management, 21(1), 1.

Rodney, Nicole C., and Connie J. Mulligan. "A biocultural study of the effects of maternal stress on mother and newborn health in the Democratic Republic of Congo." American journal of physical anthropology 155, no. 2 (2014): 200-209.

Romo, A., R. Carceller, and J. Tobajas. "Intrauterine growth retardation (IUGR): epidemiology and etiology." Pediatric endocrinology reviews: PER 6 (2009): 332-336.

Rondo, P. H. C., Ferreira, R. F., Nogueira, F., Ribeiro, M. C. N., Lobert, H., & Artes, R. (2003). Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. European Journal of Clinical Nutrition, 57(2), 266–272.

Ross, W. R., & McGill, J. B. (2006). Epidemiology of obesity and chronic kidney disease. Advances in chronic kidney disease, 13(4), 325-335.

Rowland, M. G. M., & McCollum, J. P. K. (1977). Malnutrition and gastroenteritis in the Gambia. Transactions of the Royal Society of Tropical Medicine and Hygiene, 71(3), 199–203.

Rowland, M. G. M., and J. P. K. McCollum. "Malnutrition and gastroenteritis in the Gambia." Transactions of the Royal Society of Tropical Medicine and Hygiene 71, no. 3 (1977): 199-203.

Rowland, M. G. M., Cole, T. J., & Whitehead, R. G. (1977). A quantitative study into the role of infection in determining nutritional status in Gambian village children. British Journal of Nutrition, 37(3), 441–450.

Sandman, C. A., Glynn, L., Schetter, C. D., Wadhwa, P., Garite, T., Chicz-DeMet, A., & Hobel, C. (2006). Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): Priming the placental clock. Peptides, 27(6), 1457–1463.

Sarkar, P., Bergman, K., O'Connor, T. G., & Glover, V. (2008). Maternal antenatal anxiety and amniotic fluid cortisol and testosterone: possible implications for foetal programming. Journal of Neuroendocrinology, 20(4), 489-496.

Sawyer, A., Ayers, S., Smith, H., Sidibeh, L., Nyan, O., & Dale, J. (2011). Women's experiences of pregnancy, childbirth, and the postnatal period in The Gambia: A qualitative study: Pregnancy and childbirth in The Gambia. British Journal of Health Psychology, 16(3), 528–541.

Schnider, Kimberly R., Jon D. Elhai, and Matt J. Gray. "Coping style use predicts posttraumatic stress and complicated grief symptom severity among college students reporting a traumatic loss." Journal of Counseling Psychology 54, no. 3 (2007): 344.

Scholl, T. O. (2005). Iron status during pregnancy: setting the stage for mother and infant. The American Journal of Clinical Nutrition, 81(5), 1218S–1222S.

Sear, R. (2006). Size-dependent reproductive success in Gambian men: Does height or weight matter more? Biodemography and Social Biology, 53(3–4), 172–188.

Sear, R. (2007). The impact of reproduction on gambian women: Does controlling for phenotypic quality reveal costs of reproduction? American Journal of Physical Anthropology, 132(4), 632–641.

Sear, R., Allal, N., & Mace, R. (2004). Height, marriage, and reproductive success in Gambian Women. Socioeconomic Aspects of Human Behavioral Ecology, 23, 203–224.

Sear, R., Mace, R., & McGregor, I. A. (2000). Maternal grandmothers improve nutritional status and survival of children in rural Gambia. Proceedings of the Royal Society B: Biological Sciences, 267(1453), 1641–1647.

Sear, R., Mace, R., & McGregor, I. A. (2003). A life history approach to fertility rates in rural Gambia: Evidence for trade-offs or phenotypic correlations? In The Biodemography of Human Reproduction and Fertility. Kluwer Academic Publishers.

Seckl, J. R., & Holmes, M. C. (2007). Mechanisms of Disease: glucocorticoids, their placental metabolism and fetal "programming" of adult pathophysiology. Nature Clinical Practice Endocrinology & Metabolism, 3(6), 479–488.

Shams, M., Kilby, M. D., Somerset, D. A., Howie, A. J., Gupta, A., Wood, P. J., … Stewart, P. M. (1998). 11Beta-hydroxysteroid dehydrogenase type 2 in human pregnancy and reduced expression in intrauterine growth restriction. Human Reproduction, 13(4), 799–804.

Sheehan, J. T. (1998). Stress and Low Birth Weight Infants: A structural modeling approach using real life stressors. Social Science & Medicine, 47(10), 1503–1512.

Simeon D, Guralnik O, Knutelska M, Hollander E, Schmeidler J. 2001. Hypothalamic-pituitary-adrenal axis dysregulation in depersonalization disorder. Neuropsychopharmacology. 25: 793-796.

Simons, Sterre SH, Roseriet Beijers, Antonius HN Cillessen, and Carolina de Weerth. "Development of the cortisol circadian rhythm in the light of stress early in life." Psychoneuroendocrinology 62 (2015): 292-300.

SOFA Team, & Doss, C. (2011, March). The role of women in agriculture. The Food and Agriculture Organization of the United Nations.

Soubry, A., Hoyo, C., Jirtle, R. L., & Murphy, S. K. (2014). A paternal environmental legacy: Evidence for epigenetic inheritance through the male germ line: Insights & Perspectives. BioEssays, 36(4), 359–371.

Spencer, J. A., Chang, T. C., Jones, J., Robson, S. C., & Preece, M. A. (1995). Third trimester fetal growth and umbilical venous blood concentrations of IGF-1, IGFBP-1, and growth hormone at term. Archives of Disease in Childhood-Fetal and Neonatal Edition, 73(2), F87–F90.

Spielberger, Charles Donald, Richard L. Gorsuch, Robert Lushene, P. R. Vagg, and GA1983 Jacobs. Manual for the state-trait anxiety inventory (form Y): self-evaluation questionnaire. Palo Alto, CA: Consulting Psychologists Press, 1983.

Stein, C. E., Fall, C. H. D., Kumaran, K., Osmond, C., Barker, D. J. P., & Cox, V. (1996). Fetal growth and coronary heart disease in South India. The Lancet, 348(9037), 1269-1273.

Stevenson, D. K., Verter, J., Fanaroff, A. A., Oh, W., Ehrenkranz, R. A., Shankaran, S., ... & Korones, S. B. (2000). Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Archives of Disease in Childhood-Fetal and Neonatal Edition, 83(3), F182-F185.

Stewart, C. P., Oaks, B. M., Laugero, K. D., Ashorn, U., Harjunmaa, U., Kumwenda, C., … Dewey, K. G. (2015). Maternal cortisol and stress are associated with birth outcomes, but are not affected by lipid-based nutrient supplements during pregnancy: an analysis of data from a randomized controlled trial in rural Malawi. BMC Pregnancy and Childbirth, 15(1).

Stinson, S. (1985). Sex differences in Environmental sensitivity during growth and development. Yearbook of Physical Anthropology., 28, 123–147.

Stratakis, C. (2006). Cortisol and growth hormone: Clinical implications of a complex, dynamic relationship. Pediatric Endocrinology Reviews, 3(2), 333–340.

Suglia, S. F., Staudenmayer, J., Cohen, S., Enlow, M. B., Rich-Edwards, J. W., & Wright, R. J. (2010). Cumulative stress and cortisol disruption among Black and Hispanic pregnant

women in an urban cohort. Psychological Trauma: Theory, Research, Practice, and Policy, 2(4), 326–334.

Suglia, S. F., Staudenmayer, J., Cohen, S., Enlow, M. B., Rich-Edwards, J. W., & Wright, R. J. (2010). Cumulative stress and cortisol disruption among Black and Hispanic pregnant women in an urban cohort. Psychological Trauma: Theory, Research, Practice, and Policy, 2(4), 326–334.

Sundby, J. (1997). Infertility in the Gambia: traditional and modern health care. Patient Education and Counseling, 31(1), 29–37.

Sundby, J., Mboge, R., & Sonko, S. (1998). Infertility in the Gambia: frequency and health care seeking. Social Science & Medicine, 46(7), 891–899.

Susser, Ezra S., and Shang P. Lin. "Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945." Archives of general psychiatry 49, no. 12 (1992): 983-988.

Susser, M. (1981). Prenatal nutrition birthweight and psychological development: an overview of experiments quasi-experiments and natural experiments in the past decade. American Journal of Clinical Nutrition. 34(4),784-803.

Talge, N. M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: how and why?. Journal of Child Psychology and Psychiatry, 48(3-4), 245-261.

Tamir, O. (2002). Shady Practices: Agroforestry and Gender Politics in The Gambia. Culture & Agriculture, 24(2), 70–71.

Tan, H., Zhong, P., & Yan, Z. (2004). Corticotropin-releasing factor and acute stress prolongs serotonergic regulation of GABA transmission in prefrontal cortical pyramidal neurons. Journal of Neuroscience, 24(21), 5000-5008.

Teixeira, J., Martin, D., Prendiville, O., & Glover, V. (2005). The effects of acute relaxation on indices of anxiety during pregnancy. Journal of Psychosomatic Obstetrics & Gynecology, 26(4), 271-276.

Thayer, Z. M., & Kuzawa, C. W. (2011). Biological memories of past environments: Epigenetic pathways to health disparities. Epigenetics, 6(7), 798–803.

The State of the World's Children 2015: Reimagine the Future: Innovation for Every Child. UNICEF, New York, 2015.

Thorp, J. A., Jones, P. G., Knox, E., & Clark, R. H. (2002). Does antenatal corticosteroid therapy affect birth weight and head circumference? Obstetrics & Gynecology, 99(1), 101–108.

Thurnham, D. I., C. A. Northrop-Clewes, F. S. W. McCullough, B. S. Das, and P. G. Lunn. "Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants." Journal of Infectious Diseases 182, no. Supplement 1 (2000): S23-S28.

Thurnham, David I., Angela E. Cathcart, and Margaret BE Livingstone. "A retrospective investigation of thiamin and energy intakes following an outbreak of beriberi in The Gambia." Nutrients 3, no. 1 (2011): 135-151.

Tobi, E. W., Slagboom, P. E., van Dongen, J., Kremer, D., Stein, A. D., Putter, H., … Lumey, L. H. (2012). Prenatal Famine and Genetic Variation Are Independently and Additively

Associated with DNA Methylation at Regulatory Loci within IGF2/H19. PLoS ONE, 7(5), e37933.

Tomkins, A. M., Dunn, D. T., Hayes, R. J., & Bradley, A. K. (1986). Seasonal variations in the nutritional status of urban Gambian children. British Journal of Nutrition, 56(3), 533–543.

Touray, I. (2006). Sexuality and women's sexual rights in The Gambia. IDS Bulletin, 37(5), 77–83.

Trivers, R. L. & Willard, D. E. (1973). Natural selection of parental ability to vary the sex ratio of offspring. Science, 179, 90-92.

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. Journal of Psychosomatic Research, 53(4), 865–871.

Turner, P. C., Collinson, A. C., Cheung, Y. B., Gong, Y., Hall, A. J., Prentice, A. M., & Wild, C. P. (2007). Aflatoxin exposure in utero causes growth faltering in Gambian infants. International Journal of Epidemiology, 36(5), 1119–1125.

Tzschoppe, A., Struwe, E., Blessing, H., Fahlbusch, F., Liebhaber, G., Dörr, H. G., … others. (2009). Placental 11&bgr;-HSD2 Gene Expression at Birth Is Inversely Correlated With Growth Velocity in the First Year of Life After Intrauterine Growth Restriction. Pediatric Research, 65(6), 647–653.

Ulijaszek, S. (1993). Seasonality of reproductive performance in rural Gambia. In Seasonality and human ecology. Cambridge University Press.

Uller, T. (2008). Developmental plasticity and the evolution of parental effects. Trends in Ecology & Evolution. 23, 432–438.

Vaghri, Z., Guhn, M., Weinberg, J., Grunau, R. E., Yu, W., & Hertzman, C. (2013). Hair cortisol reflects socio-economic factors and hair zinc in preschoolers. Psychoneuroendocrinology, 38(3), 331–340.

Van den Bergh, Bea RH, Eduard JH Mulder, Maarten Mennes, and Vivette Glover. "Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review." Neuroscience & Biobehavioral Reviews 29, no. 2 (2005): 237-258.

van der Voorn, Bibian, Marita de Waard, Johannes B. van Goudoever, Joost Rotteveel, Annemieke C. Heijboer, and Martijn JJ Finken. "Breast-Milk Cortisol and Cortisone Concentrations Follow the Diurnal Rhythm of Maternal Hypothalamus-Pituitary-Adrenal Axis Activity." The Journal of nutrition 146, no. 11 (2016): 2174-2179.

Villain, Marion, Vincent Cirimele, and Pascal Kintz. "Hair analysis in toxicology." Clinical chemistry and laboratory medicine 42, no. 11 (2004): 1265-1272.

Vlaardingerbroek, H., Vermeulen, M. J., Carnielli, V. P., Vaz, F. M., van den Akker, C. H. P., & van Goudoever, J. B. (2014). Growth and Fatty Acid Profiles of VLBW Infants Receiving a Multicomponent Lipid Emulsion From Birth: Journal of Pediatric Gastroenterology and Nutrition, 58(4), 417–427.

Wadhwa, P. D., Entringer, S., Buss, C., & Lu, M. C. (2011). The Contribution of Maternal Stress to Preterm Birth: Issues and Considerations. Clinics in Perinatology, 38(3), 351–384.

Walraven, G., Scherf, C., West, B., Ekpo, G., Paine, K., Coleman, R., … Morison, L. (2001). The burden of reproductive-organ disease in rural women in The Gambia, West Africa. The Lancet, 357(9263), 1161–1167.

Waterland, R. A., Kellermayer, R., Laritsky, E., Rayco-Solon, P., Harris, R. A., Travisano, M., … Prentice, A. M. (2010). Season of Conception in Rural Gambia Affects DNA Methylation at Putative Human Metastable Epialleles. PLoS Genetics, 6(12), e1001252.

Webb, P., & others. (1989). Intrahousehold decisionmaking and resource control: The effects of rice commercialization in West Africa. International Food Policy Research Institute.

Wegmüller, Rita, Amat Bah, Lindsay Kendall, Morgan M. Goheen, Sarah Mulwa, Carla Cerami, Diego Moretti, and Andrew M. Prentice. "Efficacy and safety of hepcidin-based screen-and-treat approaches using two different doses versus a standard universal approach of iron supplementation in young children in rural Gambia: a double-blind randomised controlled trial." BMC pediatrics 16, no. 1 (2016): 149.

Weinstock, M. (2007). Gender differences in the effects of prenatal stress on brain development and behaviour. Neurochemical research, 32(10), 1730-1740.

Wells, J. C. (2000). Natural selection and sex differences in morbidity and mortality in early life. Journal of Theoretical Biology, 202(1), 65–76.

Wells, J. C. (2012). A critical appraisal of the predictive adaptive response hypothesis. International journal of epidemiology, 41(1), 229-235.

Willcox, D.L., Yovich, J.L., McColm, S.C. and Phillips, J.M. (1985). Progesterone, cortisol and oestradiol-17β in the initiation of human parturition: partitioning between free and bound hormone in plasma. BJOG: An International Journal of Obstetrics & Gynaecology, 92, 65-71.

Wittrup, I. (1990). Me and my husband's wife: An analysis of polygyny among Mandinka in the Gambia. Folk, 32, 117–142.

Wood, C. E., & Walker, C.-D. (2015). Fetal and Neonatal HPA Axis. In R. Terjung (Ed.), Comprehensive Physiology (pp. 33–62). Hoboken, NJ, USA: John Wiley & Sons, Inc.

Wu, G., Imhoff-Kunsch, B., & Girard, A. W. (2012). Biological Mechanisms for Nutritional Regulation of Maternal Health and Fetal Development: Maternal nutrition and healthy pregnancy. Paediatric and Perinatal Epidemiology, 26, 4–26.

Yamada, J., Stevens, B., de Silva, N., Gibbins, S., Beyene, J., Taddio, A., … Koren, G. (2007). Hair Cortisol as a Potential Biologic Marker of Chronic Stress in Hospitalized Neonates. Neonatology, 92(1), 42–49.

Yang, Hin Zhong, Jun Lan, Yan Jian Meng, Xue Jun Wan, and Dail Wen Han. "A preliminary study of steroid reproductive hormones in human hair." The Journal of steroid biochemistry and molecular biology 67, no. 5 (1998): 447-450.

Appendix A – Review of macro and micronutrients & the consequences of deficiency during pregnancy

Macronutrient	Role	Consequences of Insufficiency
Carbohydrates	Carbohydrates provide maternal and fetal energy. Sources of energy: (1) Dietary starch converted into glucose; (2) Glycogen from diet and stores in liver and muscle; (3) Glycerol from lipolysis in adipose tissue (4) Amino acids from protein degradation. Maternal glucose is transferred to the fetus through the placenta as the primary energy source and is essential for red blood cells and anti-oxidative reactions (Kalhan et al.,1979; Jobgen et al., 2006).	Maternal consequences: ketosis, neurologic damage, weight loss, weakness and fatigue, and suboptimal intestinal health Fetal consequences: growth retardation, impaired blood flow (in mother, placenta, and fetus).
Lipids	Saturated and unsaturated fatty acids can be synthesized from glucose and amino acids in the mother and fetus. Essential fatty acids must come from the maternal diet. The placenta is permeable to long-chain polyunsaturated fatty acids and can transport essential fatty acids to the fetus. These are essential to maintaining membrane fluidity and permeability, and provide metabolic fuel for liver, skeletal muscle, and heart (Enke et al., 2008; Carlson et al., 2009; Stein et al., 2010; Imhoff-Kunsch et al., 2011).	Maternal consequences: weight loss, hyperglycemia. Fetal consequences: impaired growth and development of organs, specifically brain, eyes, and heart. Additionally, lipid deficiency may result in vitamin deficiency due to impaired absorption in the small intestine.
Protein	Some amino acids can be synthesized from essential amino acids provided by maternal diet. There are multiple transfer systems in the uterus and placenta for amino acids. Uptake of glutamine, glutamate, and others are transferred to the fetus by swallowing amniotic fluid. Amino acids are the building blocks of proteins and peptides, precursor to nitrogenous hormones, DNA, neurotransmitters, and vasodilators (Wu, 2009; Wu et al., 2011; Wu et al., 2012).	Maternal consequences: neurological damage, anemia, weight loss, impaired blood flow, weakness and fatigue, intestinal atrophy, kidney dysfunction, and cardiac failure. Fetal consequences: impaired brain development, organ maturation, and overall growth retardation.

	They also provide metabolic fuel for the small intestine, immune system, and fetal growth (Wu et al., 2009 & 2011; Wu, 2010).	

Table A1: Summary of macronutrients and their roles in the body during pregnancy and consequences of insufficiency for the mother and fetus. All information not specifically cited comes from Baschat, 2004 and Wu et al., 2012.

Micronutrient	Role	Consequence of Deficiency
Vitamin A	Growth and differentiation of cells and tissue. Fetal liver and placenta acquire and store vitamin A; mother's stores are mobilized when needed as a compensatory mechanism (Cetin et al., 2010; Gernand et al., 2016)	Vitamin A deficiency has been investigated in relation to stillbirth and low birth weight, but the effects of supplementation are unclear (Ross, 2006; McCauley, 2015).
Vitamin B6	Vitamin B6 is used in metabolism of amino acids, lipids, one-carbon units, and glycogen as a coenzyme. It is used in gluconeogenesis and transmitter biosynthesis (Cetin et al., 2010).	Has been investigated in response to preeclampsia without conclusion (Macke et al., 2006; Salam, 2015), and may be involved in placental and fetal ability to mobilize and utilize protein (Cetin et al., 2010; Gernand et al., 2016).
Vitamin D	Vitamin D is necessary to maintain D_3 concentrations in the blood and support bone health by increasing calcium absorption. Important for fetal lung, brain, and bone development (Abrams, 2007; Hart et al., 2015)	Deficiency has been associated with altered fetal brain development and increased risk of schizophrenia and autism (Eyles et al., 2011), impaired birth weight and reduced neonatal growth (Leffelaar et al., 2010). Vitamin D supplementation during pregnancy was associated with decreased preterm birth and low birth weight (De-Regil, 2016). Vitamin D deficient neonates also exhibited accelerated growth during the 1st year of life (Leffelaar et al., 2010).
Folate/Folic Acid	Folate is used in DNA replication (cell cycle), and methylation of amino acids	Folate supplementation decreases risk of devastating neural tube defects and significantly improves birth weight

	cysteine and methionine (Cetin et al., 2010). Folate also supports materno-placental tissue expansion and fetal growth (Gernand et al., 2016).	(Scholl-Johnson, 2000; De-Regil et al., 2010; Lassi et al., 2013). Folic acid supplements are often given in conjunction with iron and have a positive effect on birth weight (Christian et al., 2003; Christian, 2010).
Iron	Iron bind oxygen, is active in transport and storage, metabolism, and generation of ATP (Cetin et al., 2010; Wu et al., 2012). Pregnancy strains maternal iron supply to meet maternal haemo-expansion demands: increasing red blood cells, fetal iron uptake, and deposition in fetal and placental tissue (Wu et al., 2012; Gernand et al., 2016). At high levels, iron can be toxic (Scholl, 2005).	Iron deficiency increases risk of maternal hemorrhage and maternal mortality, preterm birth and intrauterine growth restriction (Wu et al., 2012). Iron supplementation improves birth weight (Scholl, 2005; Halder, 2013), especially when given in conjunction with folic acid (Christian et al., 2003; Christian, 2010).
Zinc	Zinc is active in maternal and fetal tissue accumulation and consequently fetal growth and development. Additionally, it regulates food intake (Cetin et al., 2010; Wu et al., 2012; Gernand et al., 2016). At high levels, zinc can interfere with copper absorption (Wu et al., 2012)	Zinc deficiency has been associated with malnutrition, negative effects on immune function, intrauterine growth restriction, and low birth weight (Castillo-Durán and Weisstaub, 2003; Wu et al., 2012). Supplementation also significantly decreases risk of preterm birth (Ota et al., 2015). Zinc may have an inverse relationship with cortisol (Vaghri et al., 2013).

Table A2: Summary of select micronutrients, their roles during pregnancy and the consequences of deficiency for fetal growth and birth outcome.

Appendix B: Hair Cortisol Extraction Protocol

Protocol for Hair Extraction with Ball Mill
Sara Fardi

Weigh:

- Weigh 10 mg of hair into 2mL Eppendorf tubes
- Label tubes accordingly, if using printed labels make sure they are waterproof.
    - Label both tops and sides as an isopropanol wash may remove ink
- Record weight for each sample
    - This data will be logged onto excel sheet and used to calculate hair cortisol measurements later

Tip: For hair samples that are longer than 1-2 inches, hair can be cut or "rolled." Roll hair samples in gloved hands to ball it up prior to weighing. Be aware of any stray hairs that stick to gloves that may cause cross contamination.

- If strands of hair reach the top of the tube they can get caught, pulled out, or ineffectively ground.

Note: Prior to starting the rest of the protocol, it is suggested that the EIA Buffer used for reconstitution is made. For EIA buffer Recipe, see bottom of protocol.

Wash:

- Add 1.5 mL of pure isopropanol, swirl and drain.
    - For samples with particulates in hair, samples may be capped and gently shaken to free any stuck debris
- Repeat wash a second time
- Dry samples in fume hood overnight (drying may take up to 2 days)

Notes: When draining samples, pour the isopropanol out slowly. Hair may become dislodged from the tube and fall out. Also, consider using a paper towel to wipe any drips off the outside/lip of the tube to prevent it from washing off the ink label on the tube.

Extraction:

1. Milling:

- Hair samples must be dry prior to milling
    - If the hair is still wet/damp, it will stick to the ball and plaster to Eppendorf tube.
- Place one ball (stainless steel) into each tube and close tube.
- Place 10 samples in each of the adapter racks and secure them inside the mill
- Ball Mill should run at 25 Hz for 10 minutes.

Notes: If hair does not mill well or creates a "donut," cut down and rerun sample. If samples are not fully ground run for an additional 2 minutes.

2. Methanol and Incubation:

- Add 1mL of pure methanol to the ground hair samples and cap them
- Secure sample racks on the shaker at ~100 rpm and run overnight.

Tip: Label tubes for step 3 in down time

3. Evaporation:

- Preparation:
    - Turn on heater (°63) on microvap when you come in; temperature takes ~20 minutes to stabilize. Move needles away from hot surface.
    - Check all tubes on air generator and microvap are secure.

- Samples:
- Remove tubes from shaker and centrifuge for 10 minutes at 2500 rpm
- Remove 875uL of the supernatant to a labeled tube. (Use a new pipette tip for each sample.)
- Microvap dries down 24 samples at a time:
    - Rack samples
    - Fit drying rack over the tubes making sure that each one has a drying nozzle in it and that it is not *in* the sample, but ~ 6mm above.
    - When you are ready to dry down samples, turn on the air generator; nitrogen production will begin automatically.
        - Switch the needle valve to on.
        - Slowly increase nitrogen flow with dial—it is unlikely you will be able to see a dimple in the surface of the methanol, but it makes a soft sound when the pressure is enough (note: it shouldn't sound like boiling, that's likely too high and may result in splashing).
- Dry down ~13 minutes. Prior to removing tubes check for remaining methanol.
- Close tubes and set aside until you are ready to reconstitute.
- Turn off, unplug, and drain air generator when done.

4. Reconstitution:

- Reconstitute extract in 0.5 mL of EIA Buffer and vortex.
- Samples may be stored at -20°C or used in assay immediately.

EIA (Dilution) Buffer:

Stock A	Volume 1000 mL	Volume 500 mL	**Stock B**	Volume 1000 mL	Volume 500 mL
0.2M NaH_2PO_4	27.8 g	13.9 g	0.2M Na_2HPO_4	28.4 g	14.2 g
H_2O	1000 mL	500 mL	H_2O	1000 mL	500 mL

Notes: Chunks may have formed in NaH_2PO_4 and Na_2HPO_4. They will dissolve on mixing plate, but it may take some time. When weighing, it may be beneficial to try and break up any large bunches of the chemicals.

EIA Buffer	Total Volume 1000 mL	Total Volume 500 mL
Stock A	195 mL	97.5 mL
Stock B	305 mL	152.5 mL
NaCl	8.7 g	4.35 g
H_2O	500 mL	250 mL

- pH EIA buffer to 7.0, bottle and store at 4°C.

Appendix C: Results Statistical Tables

C.1: Birth Outcome

Table C1: Descriptive statistics of fetal hair cortisol in relation to maternal parity, socioeconomic status, infant sex, season of conception and birth. Infant fHCC expression was significantly different between infants born to multiparous and primparous mothers.

Fetal Hair Cortisol - Averages				
Sex	**Raw Mean**	**Transformed Mean**	**n**	**p-value**
Female	0.22	-0.7	98	0.32
Male	0.2	-0.73	104	
Parity	**Raw Mean**	**Transformed Mean**	**n**	**p-value**
Multiparous	0.2	-0.74	176	0.047*
Primparous	0.24	-0.64	24	
SES	**Raw Mean**	**Transformed Mean**	**n**	**p-value**
High	0.21	-0.717	43	0.9
Mid	0.2	-0.724	58	
Low	0.21	-0.723	76	
Unknown	0.22	-0.71	24	
Season of Conception	**Raw Mean**	**Transformed Mean**	**n**	**p-value**
Dry	0.22	-0.69	115	0.12
Wet	0.19	-0.74	75	
Season of Birth	**Raw Mean**	**Transformed Mean**	**n**	**p-value**
Dry	0.21	-0.73	130	0.14
Wet	0.22	-0.68	60	

Table C2: The results of a regression (Fit Least Squares) model for fHCC by sex. Note that "Month of Birth" and "Village" are unique factors to the female and male models, respectively. For females, regression strength is 0.31 (p=0.09); for males, regression strength is 0.38 (p=0.02).

Fetal Hair Cortisol - Females				**Fetal Hair Cortisol - Males**			
Effect	**Estimates**	**Error**	**p-value**	**Effect**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
Parity	-0.06	0.04	0.14	Parity	-0.07	0.04	0.09
				Total Education	0.005	0.00	0.4
Environment:				*Environment:*			
Month of Birth	--	--	0.39	Village	--	--	0.03
- May	0.2	0.09	0.03	- Keneba	0.18	0.07	0.004
				- Karantaba	-0.23		0.05
Birth Outcome:				*Birth Outcome:*			
Gestational Age	0.09	0.02	0.001	Gestational Age	-0.03	0.02	0.17
Birth Weight	-0.82	0.5	0.1	Birth Weight	-0.22	0.5	0.66
Model Strength	**n**	**R^2**	**p-value**	**Model Strength**	**n**	**R^2**	**p-value**
	93	0.31	0.09		102	0.38	0.017

Table C2b: The results of a regression (Fit Least Squares) model for fHCC for females including maternal height and change in maternal weight during the course of pregnancy. Unfortunately, there is missing data for many mothers and this creates a strong bias in the model, so these results are not being prioritized. However, this model suggests that these two factors should be included in future studies, if possible.

Fetal Hair Cortisol - Females			
Effect	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
Parity	-0.06	0.05	0.26
Maternal Height	8.0	3.0	0.02

Change in Weight	-4.8	1.6	0.01
Environment:			
Village	--	--	0.39
- Keneba	-0.17	0.07	0.04
- Manduar	-0.4	0.1	0.01
Birth Outcome:			
Gestational Age	0.09	0.02	0.0005
Birth Weight	-0.82	0.5	0.1
Model Strength	**n**	**R^2**	**p-value**
	42	0.8 (0.4)	0.07

Table C3: The results of a regression model for gestational age by sex. Note the model for females includes parity and SES, while the male model includes the "Lost a Child" category. For females, regression strength is 0.49 (p=0.003); for males, regression strength is 0.36 (p=0.01). Fetal hair cortisol is a significant effect on female gestational age.

Gestational Age - Females				**Gestational Age - Males**			
Effect	**Estimates**	**Error**	**p-value**	**Effect**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
Parity (Multiparous)	0.037	0.21	0.85	Lost a Child (N)	-0.17	0.11	0.13
SES	--	--	0.44				
Environment:				*Environment:*			
Village	--	--	0.28	Village	--	--	0.58
- Jali	-1.62	0.6	0.013				
Birth Outcome:				*Birth Outcome:*			
Birth Weight	10.54	2.3	<0.0001	Birth Weight	9.4	2.2	<0.0001
fHCC	1.7	0.7	0.021	fHCC	-0.9	0.6	0.14
Model Strength	**n**	**R^2**	**p-value**	**Model Strength**	**n**	**R^2**	**p-value**
	77	0.49	0.003		85	0.36	0.01

Table C4: The results of a regression model for birth weight by sex. Note the differential effects in months of birth and village. For females, regression strength is 0.66 (p=0.015); for males, regression strength is 0.69 (p=0.0004). Fetal hair cortisol is a significant effect on female birth weight (p=0.05).

Birth Weight - Females				**Birth Weight - Males**			
Effect	**Estimates**	**Error**	**p-value**	**Effect**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
Height	1.6	0.56	0.006	Height	0.19	0.03	0.52
SES	--	--	0.44	SES	--	--	0.57
Environment:				*Environment:*			
Month of Birth	--	--	0.29	Month of Birth	--	--	0.01
- May	0.05	0.03	0.067	- February	-0.041	0.01	0.006
				- May	0.04	0.02	0.014
				- November	-0.04	0.02	0.039
Village	--	--	0.28	Village	--	--	0.08
- Jiffarong	0.043	0.02	0.08	- Kantong Kunda	-0.06	0.02	0.007
				- Nyorro Jattaba	0.03	0.02	0.035
Birth Outcome:				*Birth Outcome:*			
Gestational Age	0.033	0.006	<0.0001	Gestational Age	0.025	0.005	<0.0001
fHCC	-0.08	0.04	0.05	fHCC	-0.004	0.03	0.89
Model Strength	**n**	**R2**	**p-value**	**Model Strength**	**n**	**R2**	**p-value**
	66	0.66	0.015		74	0.69	0.0004

C.2 Prenatal Growth Models:

Table C5: The results of a regression model for crown rump length during the third trimester of pregnancy. Birth weight, month of birth, and village effects are significant effects. Regression strength is 0.47 ($p<0.0001$).

Crown rump - Physical (32-36 Weeks GA)			
Fixed Effects	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
Height	0.02	0.01	0.13
SES	--	--	0.24
- Mid	0.005	0.002	0.05
Environment:			
Village	--	--	0.09
- Nyorro Jattaba	-0.013	0.005	0.01
Month of Birth	--	--	0.001
- February	0.01	0.004	0.02
- May	-0.02	0.005	0.0001
Birth Outcome:			
Birth Weight	0.19	0.07	<0.0001
fHCC (ng/mg)	-0.001	0.004	0.3
Model Strength	**n**	**R2**	**p-value**
	131	0.47	<0.0001

Table C6: The results of a regression model for AC during the third trimester of pregnancy. Birth weight and maternal sociodemographic factors are significant effects on AC size. Regression strength is 0.21, but is a significant model ($p<0.0001$).

Abdominal Circumference - Physical (32-36 Week GA)			
Fixed Effects	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
Lost a Child (N)	0.008	0.003	0.009
Proxy Wealth	0.0007	0.0003	0.04
Total Education (years)	-0.001	0.001	0.044
Height	0.002	0.02	0.92
Birth Outcome:			
Birth Weight	0.1	0.05	0.0007
fHCC	0.017	0.014	0.23
Model Strength	**n**	**R2**	**p-value**
	112	0.21	0.0003

Table C7: The results of a regression model for AC z-score in the third trimester of pregnancy by sex. The male model includes more maternal inputs than the female models, which is driven by maternal education and birth weight. For females, regression strength is 0.32 (p=0.35); for males, regression strength is 0.2 (p=0.057).

AC - Z-score (32-36 Week GA) - Females				**AC - Z-score (32-36 Week GA) - Males**			
Effects	**Estimates**	**Error**	**p-value**	**Effects**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
Total Education	-0.09	0.05	0.056	Proxy Wealth	-0.08	0.03	0.016
Lost a Child (N)	0.32	0.2	0.16	Lost a Child (N)	0.36	0.21	0.09
				Total Education	-0.14	0.05	0.015
				Crowding Ratio	-0.2	0.1	0.07
Environment:				*Environment:*			
Village	--	--	0.52	Month of Birth	--	--	0.29
				- October	1.5	0.65	0.026
Birth Outcome:							
Birth Weight	-6.34	3.5	0.07				
Model Strength	**n**	**R2**	**p-value**	**Model Strength**	**n**	**R2**	**p-value**
	72	0.32	0.35		125	0.2	0.057

Table C8: The results of a regression model for OFD measurements in the third trimester of pregnancy by sex. For both sexes, birth weight is significant, while month of birth effects are variable. Village effects are significant in males. For females, regression strength is 0.46 (p=0.01); for males, regression strength is 0.5 (p=0.13).

OFD - Physical (32-36 Week GA) - Females				**OFD - Physical (32-36 Week GA) - Males**			
Fixed Effects	**Estimates**	**Error**	**p-value**	**Fixed Effects**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
SES	-0.022	0.0007	0.13	Parity Category (mulitparous)	-0.05	0.01	0.003
- Low	0.014	0.007	0.06	Height	-0.03	0.03	0.31
Height	-0.36	0.27	0.19				
Parity Category (mulitparous)	-0.004	0.005	0.43				
Environment:				*Environment:*			
Month of Birth	--	--	0.39	Village	--	--	0.13
- January	0.23	0.01	0.058	- Janneh Kunda	0.03	0.02	0.06
- May	-0.023	0.01	0.059	- Kantong Kunda	0.06	0.03	0.05
- August	-0.03	0.01	0.06	- Kuli Kunda	-0.06	0.02	0.01
				- Sankandi	-0.052	0.03	0.06
				Month of Birth	--	--	0.39
				- February	0.03	0.02	0.057
Birth Outcome:				*Birth Outcome:*			
Birth Weight	0.24	0.07	0.002	Birth Weight	0.19	0.07	0.01
Model Strength	**n**	**R2**	**p-value**	**Model Strength**	**n**	**R2**	**p-value**
	64	0.46	0.012		68	0.5	0.13

Table C9: The results of a regression model for OFD z-score in the third trimester of pregnancy by sex. Village remains a significant effect on male OFD z-score along with several maternal inputs. Note the different month of birth effects. For females, regression strength is 0.32 (p=0.26); for males, regression strength is 0.7 (p=0.06).

OFD - Z-score (32-36 Week GA) – Females				**OFD - Z-score (32-36 Weeks GA) - Males**			
Fixed Effects	**Estimates**	**Error**	**p-value**	**Fixed Effects**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
SES	--	--	0.11	Proxy Wealth	0.8	0.3	0.007
Height	-21.2	14.3	0.14	Crowding ratio	0.52	0.2	0.016
Parity Category (mulitparous)	-0.32	0.28	0.26	Total Education (years)	0.08	0.06	0.2
				Height	-0.72	1.2	0.5
Environment:				*Environment:*			
Month of Birth	--	--	0.56	Village	--	--	0.6
- January	1.14	0.6	0.08	- Jattaba	-3.1	1.5	0.05
- August	-1.5	0.8	0.07	- Joli	3.1	1.5	0.06
				- Kantong Kunda	4.2	1.2	0.002
				- Manduar	-1.4	0.6	0.04
				Month of Birth	--	--	0.16
				- February	1.3	0.5	0.03
				- August	-1.4	0.6	0.04
				- October	3.7	0.9	0.0009
Birth Outcome:				*Birth Outcome:*			
Birth Weight	6.5	3.9	0.09	Birth Weight	17.1	5.2	0.003
Model Strength	**n**	**R2**	**p-value**	**Model Strength**	**n**	**R2**	**p-value**
	64	0.32	0.26		49	0.73	0.06

Table C10: The results of a regression model for BPD z-score in the third trimester of pregnancy. A combination of maternal and environmental factors and birth weight drive this model. Regression strength is 0.38 (p=0.04).

BPD Z-score (32-36 Week GA)			
Fixed Effects	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
Proxy Wealth	0.02	0.007	0.01
Total Education	0.017	0.007	0.03
Parity Category (mulitparous)	0.59	0.05	0.25
Environment:			
Village	--	--	0.2
- Keneba	-0.17	0.07	0.03
- Manduar	-0.26	0.1	0.01
Month of Birth	--	--	0.11
- April	0.36	0.13	0.008
- February	0.21	0.07	0.005
Birth Outcome:			
Birth Weight	1.54	0.6	0.009
fHCC	0.14	0.15	0.38
Model Strength	**n**	**R2**	**p-value**
	114	0.38	0.04

Table C11: The results of a regression model for HC measurements in the third trimester of pregnancy by sex. Birth weight and SES are the strongest factors in this model. Regression strength is 0.31 (p=0.002).

Head Circumference - Physical (32-36 Week GA)			
Fixed Effects	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
SES	--	--	0.14
- Low	0.007	0.004	0.06
Crowding Ratio	0.002	0.001	0.23
Lost a Child	-0.002	0.002	0.28
Environment:			
Month of Birth	--	--	0.1
Birth Outcome:			
Birth Weight	0.14	0.04	0.0003
Model Strength	**n**	**R2**	**p-value**
	114	0.31	0.002

Table C12: The results of a regression model for HC z-score in the third trimester of pregnancy. Regression strength is 0.22 (p=0.26).

Head Circumference - z-score (32-36 Week GA)			
Fixed Effects	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
Lost a Child (N)	-0.23	0.12	0.1
SES	--	--	0.17
- Mid	-0.3	0.17	0.07
Environment:			
Village	--	--	0.32
- Nyorro Jattaba	0.7	0.3	0.045
Month of Birth	--	--	0.32
- August	-0.83	0.36	0.04
Birth Outcome:			
fHCC	-0.52	0.5	0.32
Model Strength	**n**	**R2**	**p-value**
	171	0.22	0.26

Table C13: The results of a regression model for TL measurements in the third trimester of pregnancy. Maternal inputs were overall significant effects in this model. Regression strength is 0.26 (p=0.048).

TL - Physical (32-36 Week GA)			
Fixed Effects	**Estimates**	**Error**	**p-value**
Maternal Inputs:			
Parity	-0.05	0.02	0.003
Crowding Ratio	0.02	0.008	0.046
SES	--	--	0.07
-Low	0.05	0.02	0.012
Height	-0.07	0.07	0.3
Environment:			
Month of Birth	--	--	0.8
- February	0.05	0.02	0.07
Birth Outcome:			
Birth Weight	0.35	0.2	0.08
Model Strength	**n**	**R2**	**p-value**
	106	0.26	0.048

Table C14: The results of a regression model for FL measurements in the third trimester of pregnancy by sex. The female model includes total years of education and village; the male model shows significant effects of SES and fHCC. For females, regression strength is 0.35 (p=0.5); for males, regression strength is 0.39 (p=0.08).

FL - Physical (32-36 Week GA) - Females				**FL - Physical (32-36 Week GA) - Males**			
Fixed Effects	**Estimates**	**Error**	**p-value**	**Fixed Effects**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
Total Education (years)	-0.002	0.001	0.08	SES	--	--	0.05
				- Mid	-0.016	0.006	0.007
				Parity	0.01	0.007	0.24
				Height	-0.01	0.02	0.6
Environment:				*Environment:*			
Village	--	--	0.3	Month of Birth	--	--	0.39
- Kemoto	-0.05	0.02	0.06	- September	0.03	0.01	0.03
- Manduar	-0.04	0.01	0.006				
Month of Birth	--	--	0.46				
Birth Outcome:				*Birth Outcome:*			
fHCC	-0.02	0.02	0.33	fHCC	0.067	0.02	0.003
				Gestational Age	0	0.005	0.12
				Birth Weight	0.12	0.09	0.2
Model Strength	**n**	**R2**	**p-value**	**Model Strength**	**n**	**R2**	**p-value**
	84	0.35	0.5		69	0.39	0.08

Table C15: The results of a regression model for FL z-score in the third trimester of pregnancy by sex. Note the different maternal effects were included in the female and male models and the inclusion of month of birth in the model for male FL z-score. For females, regression strength is 0.43 (p=0.04); for males, regression strength is 0.42 (p=0.03).

FL - Z-score (32-36 Week GA) - Females				**FL - Z-score (32-36 Week GA) - Males**			
Fixed Effects	**Estimates**	**Error**	**p-value**	**Fixed Effects**	**Estimates**	**Error**	**p-value**
Maternal Inputs:				*Maternal Inputs:*			
Lost a Child (N)	-0.5	0.2	0.04	SES	--	--	0.01
Height	20.2	15.1	0.18	-Mid	-1.3	0.4	0.002
Total Education (years)	-0.05	0.04	0.29	Parity	0.67	0.5	0.18
				Height	-1.4	1.2	0.3
Environment:				*Environment:*			
Village	--	--	0.51	Village	--	--	0.51
-Joli	2.6	0.8	0.002	Month of Birth	--	--	0.37
- Kemoto	-3.3	1.3	0.02	- January	-1.7	0.6	0.01
				- September	2.5	0.9	0.006
Birth Outcome:				*Birth Outcome:*			
Birth Weight	-8.6	3.7	0.03	fHCC	4.5	1.4	0.003
				Birth Weight	-4.2	3.3	0.21
Model Strength	**n**	**R2**	**p-value**	**Model Strength**	**n**	**R2**	**p-value**
	67	0.43	0.04		69	0.42	0.03

Table C17: Mixed regression model results for postnatal weight by sex. Note that month of birth is only effect in the female models, and that wealth and crowding ratio are unique to female and male models, respectively. Regression strength is 0.77 for females and 0.75 for males.

Weight - Females				**Weight - Males**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*			
Proxy Wealth	-0.001	0.001	0.5	Parity (Mulitparous)	0.022	0.01	0.04
Parity (Multiparous)	0.006	0.01	0.58	Crowding Ratio	-0.008	0.004	0.04
Environment:				*Environment:*			
Month of Birth	--	--	0.26	Village	--	--	0.04
- January	0.05	0.02	0.01	- Kuli Kunda	0.047	0.02	0.01
Village	--	--	0.5	- Sankandi	0.08	0.03	0.007
-Kantong Kunda	0.17	0.06	0.009	- Kantong Kunda	-0.07	0.02	0.005
Birth Outcome:				*Birth Outcome:*			
fHCC	-0.02	0.03	0.53	fHCC	-0.07	0.03	0.04
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	0.05	0.0005	0.48	Individual (ID)	0.01	0.0004	0.8
Time	0.17	0.002	0.48	Time	0.15	0.001	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**	
	289	0.77			317	0.75	

Table C18: Mixed regression model results for postnatal weight for age z-scores by sex for both WHO and KEN populations. Strength for populations comparisons is similar. For females, regression strength is 0.69 (WHO) and 0.68 (KEN); for males, regression strength is 0.75 (WHO and KEN). Fetal hair cortisol is a significant effect (p=0.02) on weight for age z-scores in males, but not females.

Weight for Age Z-Score - Females							**Weight for Age Z-Score - Males**						
	WHO			**KEN**				**WHO**			**KEN**		
Fixed Effects	**Estimates**	**Error**	**P**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Estimates**	**Error**	**P**
Maternal Inputs:							*Maternal Inputs:*						
Parity (Multiparous)	-0.02	0.15	0.87	-0.03	1	0.84	Crowding Ratio	-0.15	0.06	0.03	-0.12	0.05	0.03
							Parity (Multiparous)	0.2	0.17	0.02	0.17	0.1	0.25
Environment:							*Environment:*						
Month of Birth	--	--	0.6	--	--	0.6	Month of Birth	--	--	0.51	--	--	0.46
- January	0.54	0.3	0.07	0.4	0.4	0.09	- June	0.6	0.3	0.05	0.46	0.2	0.06
- June	-0.68	0.4	0.07	-0.54	0.3	0.09	Village	--	--	0.04	--	--	0.02
Village	--	--	0.4	--	--	0.35	- Kuli Kunda	0.65	0.3	0.04	0.047	0.02	0.01
- Jali	-1.1	0.5	0.03	-1.1	0.5	0.03	- Kantong Kunda	-1.2	0.4	0.005	-0.07	0.02	0.005
- Kantong Kunda	2.14	0.8	0.01	2.03	0.7	0.005	- Sankandi	1.5	0.5	0.003	0.08	0.03	0.007
Birth Outcome:							*Birth Outcome:*						
fHCC	-0.56	0.5	0.28	-0.47	0.4	0.28	fHCC	-1.3	0.5	0.02	-1.1	0.45	0.02
Random Effects	**Variance Ratio**	**Error**	**P**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Variance Ratio**	**Error**	**P**
Individual (ID)	1.5	0.12	<0.0001	1.4	0.1	<0.0001	Individual (ID)	1.7	0.1	<0.0001	1.7	0.08	<0.0001
Time	0.004	0.002	0.5	0.002	0.001	0.5	Time	0.01	0.004	0.5	0.001	0.002	0.6
Model Strength	**n**	**R2**		**n**	**R2**		**Model Strength**	**n**	**R2**		**n**	**R2**	

	342	0.69	331	0.68		325	0.75	325	0.75

Table C19: Mixed regression model results for postnatal height by sex. Despite any significance of effect, these data create poor models to explain and predict infant height in this population.

Height - Females				**Height - Males**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*			
Maternal Height	0.019	0.01	0.16	SES	0.17	0.1	0.25
				- High	-0.001	0.0002	0.02
Environment:				*Environment:*			
Month of Birth	--	--	0.01	Month of Birth	--	--	0.04
- February	-0.0009	0.0004	0.04	- February	0.001	0.0004	0.001
- August	0.002	0.001	0.03	- September	-0.001	4	0.001
- September	-0.001	0.0005	0.02	Village	--	--	0.06
Village	--	--	0.09	- Joli	-0.002	0.001	0.02
- Jattaba	-0.003	0.001	0.01	- Keneba	0.001	0.0004	0.003
- Karantaba	-0.002	0.001	0.01	- Nyorro Jattaba	-0.001	0.004	0.02
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	-0.18	5.00E-07	<0.0001	Individual (ID)	-0.17	4.00E-07	<0.0001
Time	0.01	5.00E-07	0.5	Time	0.013	5.00E-07	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**	
	263	-0.37			360	-0.54	

Table C20: Mixed regression model results for postnatal height for age z-scores by sex for both WHO and KEN populations. Strength for populations comparisons is similar. For females, regression strength is 0.67 (WHO and KEN); for males, regression strength is 0.66 (WHO and KEN). Here, environmental effects seem to be driving the model.

Height for Age Z-Score - Females							Height for Age Z-score - Males						
	WHO			KEN				WHO			KEN		
Fixed Effects	**Estimates**	**Error**	**P**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Estimates**	**Error**	**P**
Maternal Inputs:							*Maternal Inputs:*						
SES	--	--	0.1	--	--	0.3							
-Low	0.4	0.2	0.02										
Environment:							*Environment:*						
Village	--	--	0.5	--	--	0.7	Village	--	--	0.08	--	--	0.06
- Nyorro Jattaba	0.57	0.3	0.05				- Janneh Kunda	-0.87	0.2	0.0004	-0.59	0.2	0.002
							- Kemoto				0.69	4	0.07
							- Karantaba				-0.65	0.3	0.06
							Month of Birth	--	--	0.25			
							- October	0.7	0.35	0.03			
							- November	0.7	0.3	0.01			
Birth Outcome:							*Birth Outcome:*						
Birth Weight	4.3	1.5	0.007	3.6	1.5	0.02	Birth Weight	9.8	1.7	<0.0001	7.7	1.2	<0.0001
							fHCC	-0.58	0.4	0.16	-0.7	0.3	0.04
Random Effects	**Variance Ratio**	**Error**	**P**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Variance Ratio**	**Error**	**P**
Individual (ID)	1.2	0.1	<0.0001	1.2	0.1	<0.0001	Individual (ID)	1.7	0.08	<0.0001	1.7	0.08	<0.0001

Time	0.001	0.001	0.6	0.002	0.001	0.5	Time	0.001	0.002	0.6	0.001	0.002	0.6
Model Strength	**n**	**R2**		**n**	**R2**		**Model Strength**	**n**	**R2**		**n**	**R2**	
	326	0.67		317	0.67			341	0.66		341	0.66	

Table C21: Mixed regression model results for postnatal weight for height age z-scores by sex for both WHO and KEN populations. Strength for populations comparisons is similar. For females, regression strength is 0.57 (WHO) and 0.55 (KEN); for males, regression strength is 0.6 (WHO) and 0.58 (KEN). For males, fHCC is a significant effect only within the KEN population (p=0.03), while it trends towards significance in the WHO comparison (p=0.07), but not for females in either population comparison.

Weight for Height Z-Score WHO - Females								**Weight for Height Z-Score WHO - Males**							
WHO				**KEN**				**WHO**				**KEN**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*				*Maternal Inputs:*				*Maternal Inputs:*			
Parity-multiparous	-0.1	0.2	0.6	Parity-Multiparous	-0.07	0.1	0.6	Crowding Ratio	-0.1	0.06	0.13	Crowding Ratio	-0.08	0.05	0.07
SES	--	--	0.8	SES	--	--	0.7	SES	--	--	0.16	SES	--	--	0.15
												-High	-0.3	0.2	0.08
Environment:				*Environment:*				*Environment:*				*Environment:*			
Month of Birth	--	--	0.5	Month of Birth	--	--	0.6	Month of Birth	--	--	0.25	Month of Birth	--	--	0.24
- June	-0.9	0.4	0.05	- June	-0.67	0.3	0.04	Village	--	--	0.08	Village	--	--	0.03
Village	--	--	0.9	Village	--	--	0.9	- Nyorro Jattaba	-0.68	0.2	0.05	- Nyorro Jattaba	-0.57	0.2	0.026
								- Sankandi	1.2	0.5	0.008	- Sankandi	1.1	0.3	0.003
Birth Outcome:				*Birth Outcome:*				*Birth Outcome:*				*Birth Outcome:*			
fHCC	-0.52	0.6	0.4	fHCC	-0.29	0.4	0.5	fHCC	-0.9	0.5	0.07	fHCC	-0.8	0.3	0.03

Random Effects	Variance Ratio	Error	P	Random Effects	Variance Ratio	Error	P	Random Effects	Variance Ratio	Error	P	Random Effects	Variance Ratio	Error	P
Individual (ID)	0.9	0.17	<0.0001	Individual (ID)	0.8	0.1	0.0002	Individual (ID)	1.7	0.1	<0.0001	Individual (ID)	0.6	0.06	0.001
Time	0.001	0.001	0.5	Time	0.004	0.003	0.5	Time	0.01	0.004	0.5	Time	0.003	0.001	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**	
	342	0.57			331	0.55			324	0.6			325	0.58	

Table C22: Mixed regression model results for postnatal head circumference growth by sex. Models were strong for both females and males (R^2=0.86). Education and birthweight were the strongest predictors of female HC size, and birth weight and village were strongest for males.

Head Circumference (Postnatal) - Females				**Head Circumference (Postnatal) - Males**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*			
Total Education (years)	0.001	0.0004	0.005	SES	--	--	0.33
Parity (Multiparous)	0.003	0.002	0.25	Parity (Multiparous)	0.002	0.002	0.4
Environment:				*Environment:*			
Village	--	--	0.2	Village	--	--	0.06
- Manduar	-0.014	0.005	0.01	- Keneba	-0.012	0.004	0.007
Month of Birth	--	--	0.7	- Manduar	-0.01	0.005	0.07
- April	0.01	0.005	0.04	Month of Birth	--	--	0.8
Birth Outcome:				*Birth Outcome:*			
Birth Weight	0.065	0.03	0.05	Birth Weight	0.13	0.04	0.001
Gestational Age	0.002	0.002	0.3	Gestational Age	0.002	0.001	0.2
fHCC	0.002	0.008	0.8	fHCC	-0.003	0.008	0.73
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	0.21	3.00E-05	0.04	Individual (ID)	0.14	2.00E-05	0.09
Time	0.31	1.00E-04	0.5	Time	0.3	1.00E-04	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**	
	282	0.86			336	0.86	

Table C23: Mixed regression model results for postnatal HC z-scores by sex for both WHO and KEN populations. Strength for populations comparisons is similar. For females, regression strength is 0.76 (WHO) and 0.71 (KEN); for males, regression strength is 0.78 (WHO) and 0.71 (KEN). Village and month of birth effects are overall stronger for female than male HC z-scores, while birth weight is the most significant effect in the male models.

Head Circumference (Postnatal) Z-scores - Females								**Head Circumference (Postnatal) Z-scores - Males**							
WHO				**KEN**				**WHO**				**KEN**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*				*Maternal Inputs:*				*Maternal Inputs:*			
SES	--	--	0.4	SES	--	--	0.4	Crowding Ratio	-0.1	0.1	0.35	Crowding Ratio	-0.1	0.06	0.2
Parity-Multiparous	0.12	0.2	0.54	Parity-Multiparous	0.1	0.1	0.5	Parity-Multiparous	0.13	0.2	0.5	Parity-Multiparous	0.02	1	0.9
Environment:				*Environment:*				*Environment:*				*Environment:*			
Village	--	--	0.1	Village	--	--	0.1	Village	--	--	0.76	Village	--	--	0.8
- Manduar	1.1	0.4	0.02	- Manduar	-0.97	0.3	0.01	Month of Birth	--	--	0.84	Month of Birth	--	--	0.9
- Nyorro Jattaba	0.74	0.35	0.04	- Nyorro Jattaba	0.64	0	0.03								
Month of Birth	--	--	0.54	Month of Birth	--	--	0.4								
- April	0.9	0.4	0.03	- April	0.85	0.3	0.02								
Birth Outcome:				*Birth Outcome:*				*Birth Outcome:*				*Birth Outcome:*			
Birth Weight	3.5	1.9	0.08	Birth Weight	0.32	1.6	0.07	Birth Weight	8.7	2.6	0.002	Birth Weight	7.8	2.2	0.001
fHCC	-0.1	0.6	0.9	fHCC	-0.06	0.5	0.9	fHCC	-0.22	0.7	0.8	fHCC	-0.17	0.6	0.8

Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	2	0.1	<0.0001	Individual (ID)	1.4	0.1	0.0002	Individual (ID)	2.1	0.1	0.0004	Individual (ID)	2.1	0.1	0.0004
Time	0.01	0.003	0.5	Time	0.01	0.003	0.5	Time	0.01	0.004	0.5	Time	0.01	0.004	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**	
	289	0.76			289	0.71			275	0.78			275	0.71	

Table C24: Mixed regression model results for postnatal KH lengths by sex. Strength for populations comparisons is similar. For females, regression strength is 0.86; for males, regression strength is 0.88. Birth weight and environmental factors are strongest in the models.

Knee Heel Length - Females				**Knee Heel Length - Males**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*			
				SES	--	--	0.17
Environment:				*Environment:*			
Village	--	--	0.09	Village	--	--	0.06
- Karantaba	-0.02	0.01	0.02	- Janneh Kunda	-0.015	0.006	0.02
- Nyorro Jattaba	1	0.005	0.06				
Birth Outcome:				*Birth Outcome:*			
Birth Weight	0.1	0.03	0.003	Birth Weight	0.16	0.04	0.0002
fHCC	0.009	0.01	0.37	fHCC	-0.01	0.01	0.5
Random Effects	**Variance Ratio**	**Error**	**P**	Random Effects	Variance Ratio	Error	P
Individual (ID)	0.06	4.00E-05	0.29	Individual (ID)	0.16	5.00E-05	0.03
Time	0.34	3.00E-04	0.5	Time	0.35	3.00E-04	0.5
Model Strength	**n**	**R2**		Model Strength	n	R2	
	325	0.86			355	0.88	

Table C25: Mixed regression model results for postnatal MUAC growth by sex. For females, regression strength is 0.52; for males, regression strength is 0.6. Birth weight is a significant effect for both males and females, while SES, parity, and environmental effects are additionally significant effects on male MUAC growth.

Mid Upper Arm Circumference - Females				**Mid Upper Arm Circumference - Males**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*			
SES	--	--	0.6	SES	--	--	0.05
Parity (Multiparous)	-0.001	2	0.3	- Low	-0.01	0.005	0.03
				Parity (Multiparous)	0.01	0.005	0.01
Environment:				*Environment:*			
Village	--	--	0.1	Village	--	--	0.01
- Karantaba	-0.03	0.02	0.07	- Baja	0.05	0.02	0.03
				- Kantong Kunda	-0.03	0.01	0.02
				- Keneba	-0.03	0.01	0.002
				Month of Birth	--	--	0.24
				- May	-0.02	0.01	0.01
				- October	0.02	0.01	0.07
Birth Outcome:				*Birth Outcome:*			
Birth Weight	0.14	0.06	0.02	Birth Weight	0.26	0.07	0.002
fHCC	-0.007	0.005	0.7	fHCC	-0.01	0.02	0.4
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	0.05	0.0001	0.35	Individual (ID)	0.006	0.0001	0.9
Time	0.05	0.0002	0.5	Time	0.06	0.0001	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**	
	312	0.52			337	0.6	

Table C26: Mixed regression model results for postnatal MUAC z-scores by sex for both WHO and KEN populations. Strength for populations comparisons are not similar, the models for WHO stronger than those for KEN in both sexes. For females, regression strength is 0.9 (WHO) and 0.5 (KEN); for males, regression strength is 0.8 (WHO) and 0.53 (KEN). Village and month of birth effect details vary between WHO and KEN models; the amount of variation due to individual effects is greater in WHO comparisons than KEN.

MUAC Z-WHO - Females								**MUAC Z-WHO - Males**							
WHO				**KEN**				**WHO**				**KEN**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*				*Maternal Inputs:*				*Maternal Inputs:*			
SES	--	--	0.2	SES	--	--	0.7	SES	--	--	0.5	SES	--	--	0.2
Parity-Multiparous	-0.14	0.07	0.04	Parity-Multiparous	-0.05	0.03	0.07	Parity-Multiparous	-0.02	0.03	0.5	Parity-Multiparous	-0.007	0.02	0.7
Environment:				*Environment:*				*Environment:*				*Environment:*			
Month of Birth	--	--	0.5	Village	--	--	0.6	Village	--	--	0.23	Village	--	--	0.04
- November	-1.5	0.6	0.02	- Manduar	-0.97	0.3	0.009	- Kemoto	1.4	0.6	0.03	- Kemoto	0.9	0.4	0.04
				- Nyorro Jattaba	0.64	0	0.03	- Keneba	-0.9	0.3	0.01	- Keneba	-0.6	0.2	0.003
				Month of Birth	--	--	0.4	Month of Birth	--	--	0.6				
				- April	0.85	0.3	0.02								
Birth Outcome:				*Birth Outcome:*				*Birth Outcome:*				*Birth Outcome:*			
Birth Weight	2.3	3.1	0.5	Birth Weight	5.3	1.4	0.001	Birth Weight	5.2	2.5	0.04	Birth Weight	3.6	1.4	0.1
fHCC	0.01	0.9	0.9	Gestational Age	-0.2	0.07	0.008	fHCC	0.08	0.6	0.9	fHCC	0.04	0.4	0.9

				fHCC	0.1	0.4	0.8								
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	6.8	0.4	<0.0001	Individual (ID)	0.3	0.06	0.01	Individual (ID)	2	0.1	<0.0001	Individual (ID)	0.34	0.05	0.002
Time	0.004	0.002	0.5	Time	0.02	0.02	0.5	Time	0.004	0.001	0.5	Time	0.02	0.01	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**	
	225	0.9			304	0.5			264	0.8			359	0.53	

Table C27: Mixed regression model results for postnatal TSF test results by sex. For males and females, regression strength is 0.45. Village and parity effects are significant in the male model of TSF measurements, while gestational age and SES have the strongest significance in the female model of TSF measures.

Triceps Skin Fold - Females				**Triceps Skin Fold – Males**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*			
SES	--	--	0.3	SES	--	--	0.2
- Low	-0.02	0.01	0.06	Parity (Multiparous)	0.03	0.01	0.03
Environment:				*Environment:*			
Village	--	--	0.8	Village	--	--	0.06
				- Keneba	-0.08	0.02	0.002
				- Baja	0.16	0.06	0.01
				Month of Birth	--	--	0.9
				-May	-0.06	0.02	0.01
Birth Outcome:				*Birth Outcome:*			
Gestational Age	-0.02	0.006	0.004	Birth Weight	0.26	0.2	0.16
fHCC	0.03	0.04	0.4	fHCC	0.06	0.04	0.2
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	0.25	0.001	0.004	Individual (ID)	0.16	0.0006	0.05
Time	0.02	0.0002	0.5	Time	0.01	0.0002	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**	
	379	0.45			337	0.45	

Table C28: Mixed regression model results for postnatal TSF test results by sex for both WHO and KEN populations. Strength for populations comparisons are not similar; as with MUAC z-scores, models for WHO z-scores are stronger. For females, regression strength is 0.79 (WHO) and 0.46 (KEN); for males, regression strength is 0.76 (WHO) and 0.43 (KEN). Village effects are variable between WHO and KEN models. Overall, Gestational age and parity are significant effects on female TSF z-scores; village has significant effects on male TSF z-scores.

Triceps Skin Fold Z-scores - Females								**Triceps Skin Fold Z-scores - Males**							
WHO				**KEN**				**WHO**				**KEN**			
Fixed Effects	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**	**Fixed Effects**	**Estimates**	**Error**	**P**
Maternal Inputs:				*Maternal Inputs:*				*Maternal Inputs:*				*Maternal Inputs:*			
SES	--	--	0.5	Parity (Multiparous)	-0.05	0.02	0.03	SES	--	--	0.6	SES	--	--	0.4
Parity (Multiparous)	-0.1	0.05	0.1					Parity (Multiparous)	0.02	0.04	0.6				
Environment:				*Environment:*				*Environment:*				*Environment:*			
Village	--	--	0.7	Village	--	--	0.1	Village	--	--	0.2	Village	--	--	0.2
				- Karantaba	-0.63	0.2	0.06	- Baja	1.6	0.9	0.07	- Keneba	-0.5	0.2	0.01
				- Nyorro Jattaba	0.43	0.2	0.02	Month of Birth	--	--	0.9	Month of Birth	--	--	0.3
								- May	-0.7	0.3	0.03	- May	-0.4	0.2	0.05
Birth Outcome:				*Birth Outcome:*				*Birth Outcome:*				*Birth Outcome:*			
Gestational Age	-0.4	0.1	0.004	Gestational Age	-0.2	0.06	0.005	Gestational Age	-0.1	0.1	0.4	Gestational Age	-0.03	0.1	0.7

Birth Weight	2.8	2.6	0.3	Birth Weight	32	1.6	0.07	Birth Weight	3.1	2.9	0.3	Birth Weight	2.5	1.7	0.1
fHCC	0.6	0.7	0.3	fHCC	-0.06	0.5	0.9	fHCC	0.25	0.6	0.7	fHCC	0.03	0.3	0.9
Random Effects	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**	**Random Effects**	**Variance Ratio**	**Error**	**P**
Individual (ID)	2	0.18	<0.0001	Individual (ID)	1.4	0.1	0.0002	Individual (ID)	1.6	0.1	<0.0001	Individual (ID)	0.24	0.04	0.02
Time	0.02	0.01	0.5	Time	0.01	0.003	0.5	Time	0.02	0.01	0.5	Time	0.01	0.006	0.5
Model Strength	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**		**Model Strength**	**n**	**R2**	
	232	0.79			304	0.46			264	0.76			338	0.43	