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Biological memories of apartheid: Intergenerational effects of prenatal and early life stress and trauma on birth outcomes, HPA axis function, and mental health in Soweto, South Africa

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ABSTRACT

Biological memories of apartheid:
Intergenerational effects of prenatal and early life stress and trauma on birth outcomes, HPA axis function, and mental health in Soweto, South Africa

Andrew Wooyoung Kim (김우영)

South Africa's rates of mental, neurological, and substance use disorders are among the highest in sub-Saharan Africa. In 2016, the estimated 12-month prevalence for any psychiatric disorder was 16.2%, or approximately 9.1 million individuals. Despite these elevated rates of psychiatric morbidity, access to mental health treatment is poor: only 27% of patients living with severe mental illness are expected to receive treatment. The current state of public mental health in South Africa is foregrounded by a long and recent history of institutionalized White supremacist policies implemented during the Apartheid regime (c. 1948-1994).

Since South Africa's democratic transition, nationalist ideologies promoting aspirations for unity, equality, and freedom in the new "rainbow nation" have continuously been met with chronicities of anti-black violence, misogynoir, and structural violence, all of which are known risk factors for psychiatric disorders. These legacies of white supremacist apartheid policies underpin the dramatic inequities seen in mental health disparities. In addition to these ongoing societal effects, there is growing evidence that the stressors of the past could have lingering biological effects that continue to influence and mental health across the lifecourse.

Growing evidence from the fetal origins of health and disease framework shows that past stress and trauma exposures, particularly those that occur during early development, can durably alter the development and function of various stress regulatory mechanisms in humans. Among reproductively aged women, these long-term impacts could shape the gestational environment

experienced by the next generation, thereby influencing grandoffspring development. Thus, maternal exposures during gestation may not only affect their developing children but also affect the health and biology of subsequent generations - thus describing a possible intergenerational mechanism for stress transmission.

While the sustained and deleterious effects of prenatal stress and cortisol exposure are increasingly evident, it is not yet clear the extent to which their long-term and intergenerational impacts on stress physiological function, specifically the hypothalamic-pituitary-adrenal (HPA) axis are reversible. Very early findings suggest that positive developmental conditions can ameliorate the durable effects of past trauma on the HPA axis. Scientists have thus far been unable to test this hypothesis, however, because there are very few longitudinal studies that directly assess maternal exposures to stress and trauma during pregnancy and that span multiple generations.

Drawing from data from a 30-year multigenerational birth cohort study based in Soweto and 21 discontiguous months of ethnographic research with mental health patients, professionals and NGOs in South Africa between June 2017-October 2020, this dissertation examines the biocultural transmission of embodied trauma from apartheid and its impacts on human biology and mental health in subsequent generations among families in Soweto, South Africa. I draw on two separate longitudinal cohort studies based in Soweto and a comparative study in Cebu, Philippines to examine the intergenerational and lifecourse impacts of early life stress during prenatal development and childhood.

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LIST OF ABBREVIATIONS

List of abbreviations

1G: First generation
2G: Second generation
3G: Third generation
ACTH - adrenocorticotropic hormone
AM: Morning
ANOVA - Analysis of variance
BMI – Body mass index
BT20: Birth to Twenty
CI: confidence interval
CRH - Corticotropin-releasing hormone
CRP – C-reactive protein
DHS – Demographic and Health Survey
DOHaD – Developmental origins of health and disease
DPHRU: Developmental Pathways for Health Research Unit
GDP – Gross domestic product
HAZ – Height for age z-score
HPA axis: Hypothalamic Pituitary Adrenal Axis
IRB – Institutional Review Board
ng: nanograms
PM: Evening
PTSD: Post traumatic Stress Disorder
RA – Research assistant
SAMRC: South African Medical Research Council
SAM: Sympathetic Medullary-Adrenal axis
SD – Standard deviation
SES – Socioeconomic status
TSST: Trier Social Stress Test
USD – United States Dollar
WAZ – Weight for age z-score
WHO – World Health Organization

DEDICATION

To my father, Dr. Yong-Kyu Kim, a geneticist and evolutionary biologist whose insatiable academic curiosity, work ethic, and deep commitment to science provided a better life for our family and instilled these same morals, ethics, and values in his son.

And to *Drosophila melanogaster*.

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CHAPTER 1 – Introduction & Dissertation Outline

1.1 Introduction

In 1994, South Africa's nearly 50 year history of white supremacist rule under the colonial *Apartheid* government ended in a successful movement for decolonization. Yet since the region's pre-apartheid years and despite the people's laborious struggle for a new democratic nation, South Africa continues to see the lasting legacies of social inequality, systematic racialized violence, and historical trauma recapitulate into the present day. In a country characterized by its abhorrent racial, geographic, and socioeconomic inequalities, South Africa reports elevated rates of infectious and non-communicable diseases that follow along these historical patterns of subjugation. The nation's first nationally representative survey of mental health published in 2004 reported high morbidity and future risk for a wide range of psychological and psychiatric disorders (Herman et al. 2009). Furthermore, South Africa's recent rates of mental, neurological, and substance use disorders are among the highest in sub-Saharan Africa – in 2016, the estimated 12-month prevalence for any psychiatric disorder was 16.2%, or approximately 9.1 million individuals (GBDCN 2017). Despite these elevated rates of psychiatric morbidity, access to mental health treatment continues to be a concern: only 27% of patients living with severe mental illness are expected to receive treatment (Herman et al. 2009) in a national public mental health system that is overwhelmingly overburdened and under-resourced (Docrat et al. 2019).

The toxic conditions commonly experienced across societies afflicted by colonialism and structural violence are well-known risk factors for mental illness, including poverty (Lund et al. 2011), food insecurity (Weaver & Hadley 2009), perceived inequality and discrimination (Lin et al. 2011; Pieterse et al. 2012), and violence (Fowler et al. 2009; Punamäki 1988). In particular,

psychosocial stress and trauma are well-known risk factors for the development, duration, and severity of psychopathologies across the lifecourse, a set of findings that has held consistent across cultural contexts and populations (Kran et al. 2015; Mandelli et al. 2015; Ozer et al. 2003). The racist, classist, and misogynist histories of South African apartheid and its ongoing legacies are no exception (Crais 2011; Gqola 2007; Lockhat & Van Niekerk 2000). The first set of apartheid laws prohibited marriage and sexual relations across "racial" lines (Prohibition of Mixed Marriages Act of 1949 and the Immorality Amendment Act of 1950) and closely after, produced the social technology of "racial" classification (Population Registration Act of 1950) that classified South Africans into one of four groups: "Black," "Coloured," "Indian," and "White" (along with sub-classifications). These early hegemonic policies created an opportune set of political justifications and social logics to authorize the mass evictions and segregations of communities, economic oppression, systematic police brutality and militarization, blatant prejudice, and gross human rights violations characteristic of life under the apartheid regime for the country's non-white majority.

While the end of the apartheid regime and the election of Nelson Mandela through the country's first democratic election brought widespread hope for a "new South Africa" in 1994, critics across South African society argue that the transition into independence created a false sense of closure to the violent systems of oppression produced by the apartheid state. South Africa is globally recognized as the world's most unequal country, whose societal gaps are filled with numerous national campaigns against gender-based violence and femicide (Abrahams et al. 2013; Mogale et al. 2012; Nowrojee 1995), stretched by growing economic disparities (Bhorat & Van der Westhuizen 2010), and dug deeper with every new mineral mine excavated for gold, diamonds, and profit for the country's elite (Davenport 2013). The racist legacies of South

Africa's past continue to manifest into the everyday realities of the present. In one nationally-representative study, all Black[1] communities were two to four times more likely to experience acute and chronic racial discrimination relative to Whites (Williams et al. 2008). Additionally, perceived chronic racial discrimination was found to adversely affect mental health after controlling for demographics, stress, psychological dynamics, and socioeconomic status (SES) (Williams et al. 2008). Finally, injuries and violence represent South Africa's leading cause of death and lost disability-adjusted life years (Seedat et al. 2009). In sum, present day South African society continues to be plagued by the persistent societal institutions of apartheid, including chronic poverty (Gibbs et al. 2018), discrimination (Williams et al. 2008), and racialized inequality (Adjaye-Gbewonyo et al. 2016; Burns 2015), all of which are known risk factors for psychiatric morbidity across the lifecourse (Allen et al. 2014; Moomal et a. 2009; Myer et al. 2008).

In addition to these adverse social, political, economic impacts on mental health, growing evidence in South African communities and other populations suggest that the psychosocial stress and traumatic experiences from the past may have durable impacts on biological function and psychological status across the lifecourse (Kuzawa & Sweet 2009; Mandelli et al. 2015; Miller et al. 2011; Taylor et al. 2010). Recent studies show that past experiences of stress and trauma, particularly those that occur during early human development, can have sustained impacts on the development and function of various stress regulatory mechanisms in humans, including the cardiovascular system, neurobiological function, and neuroendocrine pathways (Taylor et al. 2010; Heim et al. 2019). Furthermore, in reproductively-aged women, the effects of

[1] In this study, Black was a racial classification used to refer to all historically marginalized groups in South Africa used by the Black Consciousness Movement in South Africa in the 1960s, including Africans, Coloureds, and Indians (Subreenduth 2003).

early experience on later life physiological status in future mothers could in turn biologically modify the mother's intrauterine environment of the developing fetus and thus have impacts that extend across multiple generations (Drake et al. 2004; Kuzawa & Sweet 2009). In sum, the long-term effects of early developmental stress and trauma exposure, stemming possibly as far back as intrauterine development and thus tied to the mother's gestational experiences, may manifest across the lifecourse, affect later-life physiology and health, and alter the intrauterine environment of the next generation – thus creating a potential intergenerational pathway of stress transmission and mental illness risk. This central question is the focus of this dissertation.

In addition to the growing literature suggesting the possibility of the intergenerational mental health impacts of prenatal stress and trauma, scientists know even less about the ameliorative factors that may buffer and reverse the sustained psychiatric impacts of intergenerational trauma and the psychobiological pathways that underlie trauma reversal. Unfortunately, most studies on mental illness have been conducted in high-income, Western countries despite the fact that mental illnesses are more prevalent and severe in low- and middle-income (LMIC), non-Western contexts (Rebello et al. 2014), thus limiting the potential for evidence-based public health interventions. Integrating biological, epidemiological, and anthropological theories and methods, my dissertation examines the intergenerational effects of psychological trauma, its impacts on psychiatric disease risk, and whether the biological pathways that perpetuate the long-term effects of intergenerational trauma are reversible through culturally-resonant social interventions in post-apartheid South Africa.

My research is motivated by my experience as a child of Korean immigrants and a grandchild of Korean War survivors. My parents immigrated to the United States from South Korea in the late 80's in search of political stability and socioeconomic opportunity. While they

did not come to the US with much, my parents brought with them generational memories of colonialism, the heavy burdens of historical trauma from deep poverty, militarized occupation, and their experiences of growing up in a precarious post-war society. As I grew older and became aware of such violent histories, I wondered how the phantoms of my family's past could continue to haunt us in the future. How did my ancestors, grandparents, and parents endure and overcome such oppressive conditions, and could the cumulative trauma they embodied overtime reverberate across multiple generations and affect me? My family's experience with political violence, trauma, and illness generated my abiding curiosities in the biology of generational trauma and resilience and the human capacity to overcome systemic oppression. I pursued these interests in college where I studied the genetics of adult PTSD (Smith et al. 2013) and the intersections of culture, religion, and mental health in rural Haiti. Deeply fascinated in the interplay between biology and culture, I combined my interests in the biology of trauma with critical theories on global oppression and racial violence to develop my current doctoral dissertation based in post-apartheid South Africa.

Drawing from data from a 30-year multigenerational birth cohort study based in Soweto and 21 discontiguous months of ethnographic research with mental health patients, professionals and NGOs in South Africa between June 2017-October 2020, this dissertation examines the biocultural transmission of embodied trauma from apartheid and its impacts on human biology and mental health in subsequent generations among families in Soweto, South Africa. This dissertation draws upon three separate longitudinal cohort studies based in Soweto to examine the intergenerational and lifecourse impacts of early life stress during prenatal development and childhood.

My findings show that maternal prenatal stress experienced during the violent dissolution of apartheid in 1990, when interacted with younger maternal age and greater past stress exposure, predicts worse psychiatric morbidity during late adolescent 17-18 years later. Additionally, I report that greater severity of childhood trauma is associated with stronger positive associations between self-perceived COVID-19 infection risk and depressive symptomatology. I corroborate these epidemiological trends by illustrating processes of embodiment, memory work, and structural violence that underlies intergenerational trauma, lifecourse stress, and experiences during the COVID-19 pandemic, which all shape present mental well-being. Ultimately, findings from this biocultural investigation can help strengthen the public health of historically oppressed communities and assist societies overcome the lasting consequences of intergenerational trauma.

1.2 South Africa: History, politics, and mental health

The legislative dissolution of the white supremacist apartheid regime in South Africa (Figure 1) created fertile ground for the reconstruction of a new, multiracial "rainbow nation," which sought the realization of new hopes, freedoms, and futures for South Africa's communities of color. Political and community violence, however, continued to ensue across the country, especially in Soweto (Figure 2). These periods of political unrest were fueled by strict militarized political repression of resistance movements, covert government efforts to instigate interethnic violence in black communities, and community violence over scarce resources in informal settlements (Beinhart 2001). It is estimated that approximately half the people who died due to political violence during the apartheid regime died in the last four years (1990-1994) (Beinhart 2001; Hickel 2015).

Figure 1. Map of South Africa *Figure 2.* Map of Soweto, Gauteng

Since the democratic transition in 1994 and introduction of a "new South Africa," however, anthropologists, historians, and other scholars in South Africa and across the world have thoroughly critiqued the liberal expectations of equality in South African nation building and decolonization (Fassin 2007; Makhulu 2010; Ndlovu-Gatsheni 2007). Pre-existing, apartheid-era inequities in socioeconomic status, land ownership, and mortality have barely improved within the past 26 years of democracy. Amidst these conditions, new generations of "born frees" carry the intergenerational burdens of apartheid and while traversing a post-apartheid moment characterized by precarity, violence, and inequality. The social and economic promises of an egalitarian, multiracial South Africa that "born frees" sought to revel in were never fulfilled. Anthropologists and other scholars have argued that, instead, the amalgamation of the compounding effects from cumulative historical oppression of Western imperialism, violent transitions from the racial project of apartheid to "democracy," and current anti-black and anti-poor social inequities continue to produce harmful conditions that place many at high risk for mental illness in South Africa (Gobodo-Madikizela 2012; McIsaac 2019; Volks 2014; Williams et al. 2008).

Recent estimates show that the prevalence, incidence, and burden of mental illness in South Africa are relatively high compared to other countries worldwide: about one in three (30.3%) South Africans have been diagnosed with a mental illness, over a quarter of all cases (25%) are considered severe, and nearly half of all citizens (47.5%) will experience a psychiatric disorder in their lifetime (Herman et al. 2009). Despite these conditions, mental healthcare usage and access in South Africa is severely limited, with only 27% of patients with severe mental illnesses receiving treatment, 16% of citizens enrolled in medical aid, and only 0.31 psychiatrist per 100,00 uninsured population (Docrat et al. 2019). These severe burdens of mental illness and barriers to mental healthcare necessitate critical anthropological investigation into the historical, cultural, and political economic conditions that sustain these abhorrent psychological trends. These diverse insights can also inform future social and health interventions aimed at healing trauma, reducing stigma, and coping with and preventing mental illness. As these health inequities persist across generations, elucidating the biological and sociopolitical processes that sustain the intergenerational "mental state" of South Africa can inform future social and health interventions aimed at breaking cycles of mental illness and promoting health justice.

1.3 Biology of intergenerational trauma

Researchers have long studied how stress and trauma disrupt stress sensitive physiological mechanisms such as the hypothalamic-pituitary-adrenal (HPA) axis, a key system that regulates our adaptive response to stress through a series of tightly-regulated neuroendocrinological pathways that produce stress-sensitive signaling hormones, including cortisol. Both early and sustained experiences of social adversity such as discrimination, trauma, and poverty have been found to chronically alter cortisol production, which may lead to durable,

long-term impacts on HPA axis function (Heim & Binder 2008). High cortisol levels produce toxic neurochemical conditions in the brain that can lead to neuronal deterioration and increase the risk of mental illness (Gold et al. 2002). During pregnancy, maternal stress can alter cortisol production and raise her own circulating levels, which can cause cortisol to pass through the placenta, reach the developing fetus's brain, and affect fetal development, including the ontogeny of the HPA axis (Seckl 2004). High levels of fetal cortisol exposure can lead to poor birth outcomes (Kim et al. 2020), postnatal growth (Schneider et al. 1999), and elevate the child's risk for cortisol dysregulation and mental illness (Glover et al. 2010; Thayer et al. 2018).

While the sustained and deleterious effects of prenatal stress and cortisol exposure are increasingly evident (Pearson et al. 2015), it is not yet clear the extent to which their long-term and intergenerational impacts on HPA axis function are reversible. Very early findings suggest that positive psychosocial experiences such as a strong sense of belonging, ethnic identity, and social support, particularly during adolescence, can ameliorate the "programming" effects of past trauma on the HPA axis (Gunnar et al. 2019). The HPA axis undergoes major rewiring during the widespread hormonal changes that coordinate puberty, a period in which positive psychosocial experiences may have disproportionately positive impacts on cortisol regulation (Gunnar et al. 2019; Hostinar et al. 2015). Scientists have thus far been unable to test this hypothesis, however, because there are very few longitudinal studies that directly assess maternal exposures to stress and trauma during pregnancy and that span multiple generations.

1.4 Biological memories of apartheid: a dissertation

The overarching goal of this dissertation is to examine the intergenerational and early life impacts of prenatal stress and trauma exposure on mental illness risk and HPA axis function in

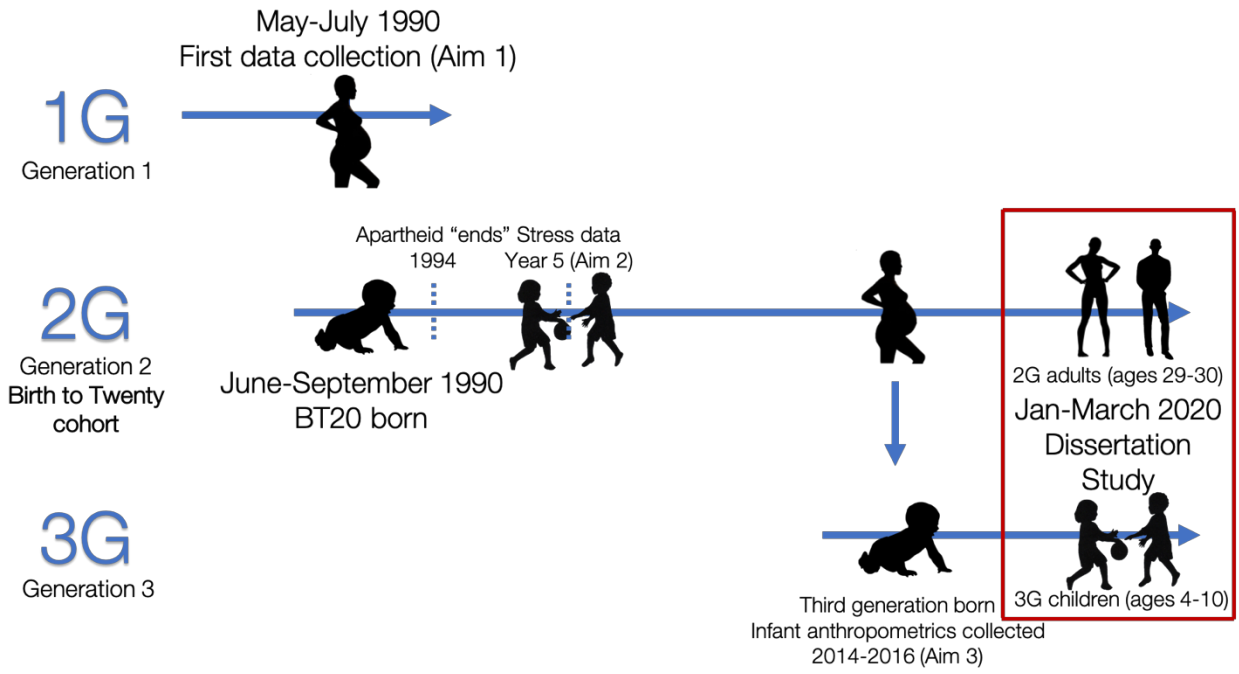
second generation children and third generation grandchildren in Soweto, South Africa (Figure 3). The first aim of this study is to examine 1) how prenatal stress experienced gestating mothers (1G) affects mental illness risk (e.g. depression, anxiety, PTSD), and HPA axis dysfunction (e.g. cortisol and inflammation) among second-generation (2G) offspring exposed to maternal stress *in utero*. The second aim of this study is to examine 2) how early life, postnatal stress exposure affects mental illness risk, and HPA axis dysfunction (e.g. cortisol and inflammation) among second-generation (2G) offspring. The third aim of this study is to 3) examine how prenatal stress and early life stress exposure affects poor birth outcomes, mental illness, and HPA axis dysfunction (e.g. cortisol and inflammation) among third-generation (3G) offspring unexposed to the initial prenatal stress experienced by their grandmother (1G). I assess these aims using the Birth to Twenty (BT20) study, a 30-year longitudinal and multigenerational study run by the South African Medical Research Council (SAMRC) and the Developmental Pathways for Health Research Unit (DPHRU) at Chris Hani Academic Baragwanath Hospital located in Soweto, South Africa. This ongoing, longitudinal birth cohort stands as Africa's largest and longest running study of its kind and one of the few large-scale, multigenerational studies in the world (Richter et al. 2007). BT20 provides the only birth cohort study in South Africa to study the generational impact of apartheid on health and physiology in African communities.

To examine the intergenerational mental health effects of the apartheid-based trauma, I leverage over 30 years of existing, epidemiological data and new primary data across three generations of families from BT20. My ongoing study, called the Soweto Stress Study (n=400), follows up on 200 2G women who were exposed as fetuses to the dissolution of the apartheid government in 1990 and their 3G children who were born in the past 5-10 years. In 1990, 1G pregnant women completed a survey about experiences with trauma, discrimination, and political

violence from apartheid during their third trimester. Thirteen years after birth, 2G adolescents completed a measure assessing the strength of their social support systems, including peer and family support and feelings of societal inclusion. I compare these data on maternal prenatal stress against various markers of health among 2G women and 3G grandchildren, including birth outcomes (e.g. birthweight, preterm birth status), mental illness risk (e.g. depression, anxiety, PTSD), and HPA axis function, specifically cortisol collected from saliva and inflammation levels found in blood. To analyze the potential reversibility of maternal trauma exposure, I will examine whether greater levels of adolescent social support reduce future mental illness risk and regulate HPA axis function in both 2G women and 3G children.

Prior to launching this wave of data collection in January 2020, between June 2017 and December 2019, I conducted over 12 months of interviews, focus groups, and ethnography with psychiatric patients, health professionals, and mental health NGOs to immerse myself to the historical, social, and political dynamics of physical and mental health in Soweto (Kim et al. 2019; Kim 2020; Mendenhall & Kim 2019) (Figure 2). This in-depth qualitative research considerably strengthened the design and implementation of my current study. For instance, I adapted existing survey items and included new questions to make them more culturally relevant to local perspectives of mental health in Soweto and developed a new scale on coping behaviors (Kim et al. in prep) as most psychological screeners are developed for high-income, Western populations. I also forged relationships with local psychosocial support NGOs to train my staff in psychological first aid and co-created a referral system for study participants who presented with severe mental illness and suicide.

Figure 3. Outline of dissertation data collection from Birth to Twenty



1.5 The 2019 Coronavirus Pandemic

On 26 March 2020, the South African government imposed a national lockdown that prohibited citizens from leaving a strict quarantine except for food, medicine, and essential work. In-country travel and the sale of alcohol and cigarettes were also banned. The country was praised by the World Health Organization for its swift and assertive efforts to slow the transmission of the 2019 coronavirus (SARS-CoV-2) disease (COVID-19) (WHO 2020). Yet others, including the United Nations, criticized the government for its harsh sanctions against non-adherent communities. Police brutality, militarization, and demolition of informal settlements brutalized households across the country, especially in already marginalized communities that lack adequate resources to properly adhere to quarantine laws. Amidst ongoing conditions of racialized inequality, South Africa's harsh administration of its national lockdown

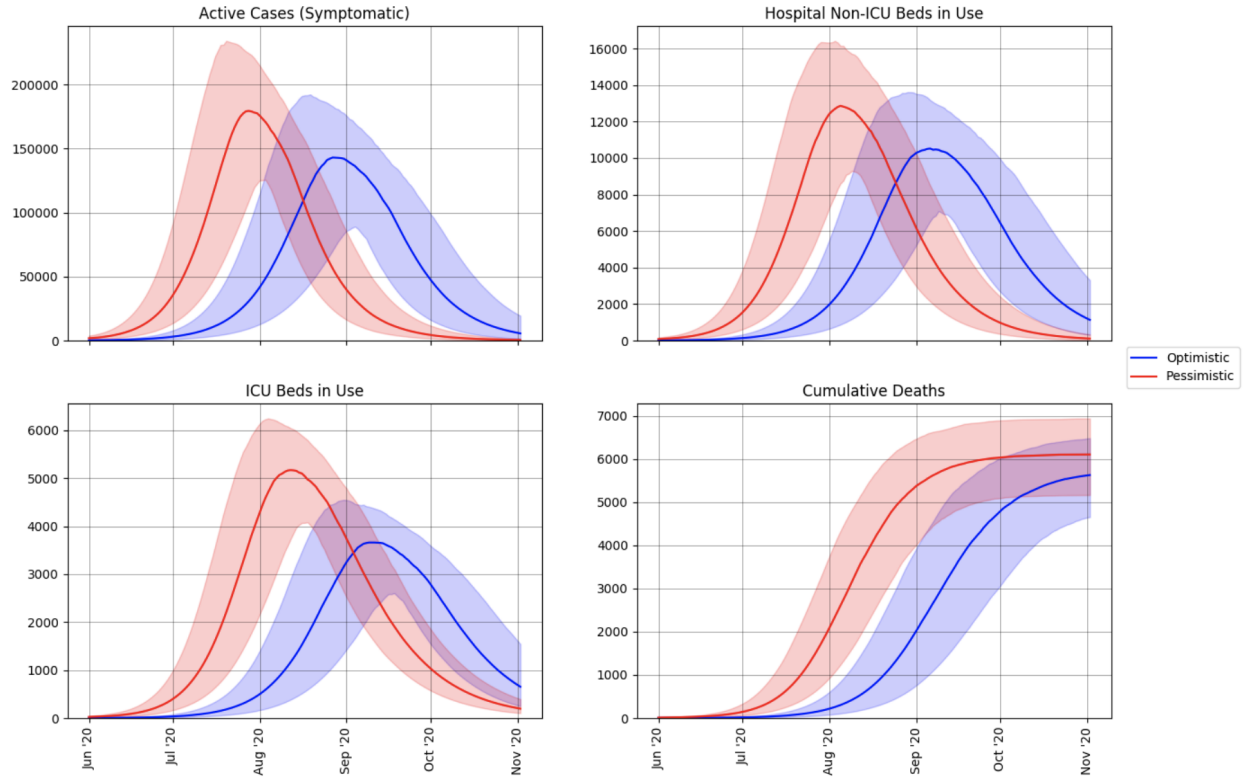
has introduced serious threats to public mental health (Kim et al. 2020a; Reddy et al. 2020) in a society where one in three individuals develop a psychiatric disorder during their life (Herman et al. 2009).

Data from past coronavirus epidemics (e.g. SARS, MERS) poignantly illustrate the psychosocial impacts of quarantine and foreshadow the possible psychological consequences of South Africa's lockdown. Numerous aspects of life under quarantine, including emotional distress, social isolation, and for some, extreme threats to survival, may substantially increase psychiatric risk (Brooks et al. 2020; Jung & Jun 2020). Emerging epidemiological data on COVID-19 worldwide corroborate these findings and report greater psychiatric morbidity and barriers to accessing mental healthcare (Brooks et al. 2020; Jung & Jun 2020). Additionally, early evidence on hospitalized cases of COVID-19 reports novel psychopathological presentations among COVID-19 patients, including anxiety, psychosis, and mood disorders (Subramaney et al. 2019). In South Africa, pre-existing societal conditions including rampant poverty, unemployment, and infectious and non-communicable disease burden foregrounded by the ongoing legacies of the apartheid regime and its racial capitalist logics, place many individuals at elevated risk for COVID-19 (StatsSA 2018).

COVID-19 emerged South Africa at a time of high prevalence of mental illness and low healthcare access: over a quarter of all cases are considered severe (Herman et al. 2009), yet only 27% of patients with severe mental illnesses receiving treatment and 16% of citizens enrolled in health insurance (Docrat et al. 2019). Amidst these conditions, rates of new COVID-19 cases continue to rise in South Africa - epidemiological models estimate the pandemic will peak between July and September 2020 (SACMC 2020) (Figure 4). As the total prevalence and rate of

COVID-19 infections approaches an all-time high, a growing psychological burden due to socioeconomic, medical, and political adversities is expected.

Figure 4. Epidemiological models of the COVID-19 pandemic, associated healthcare burdens, and mortality in South Africa (SACMC 2020).



Note: These models were released in a public report on 6 May 2020. Models are subject to change with more data overtime.

Dissertation research before the COVID-19 pandemic

After launching data collection in January, my study assessed mental illness risk (depression, anxiety, PTSD), stress and trauma exposure, and other lifestyle and household factors among families in and around Soweto. To trace the biological mechanisms involved in facilitating the intergenerational transmittance of trauma, I also collected saliva and blood

samples to measure diurnal cortisol levels and inflammatory profiles. These new data points will be combined with 30-years of longitudinal data to understand the life course pathways that influence the development of later life psychopathologies. Before the lockdown began, we knew that thousands of families already faced enormous hardship due to the long histories of government divestment in the township and the current social and environmental conditions in Soweto (a lasting legacy of apartheid policies). The impending pandemic, however, would only magnify the increased risk for domestic violence, food insecurity, overcrowding, limited healthcare access, and poor mental health, among others.

The impacts of COVID-19 on my dissertation research

I decided to stay in South Africa to continue to oversee my study and research staff, because of adequate access to high quality private medical care, and because of South Africa's early and aggressive public health response to the pandemic, which has resulted in lower prevalence and incidence rates compared to other countries such as the United States, Italy, Mexico, Indonesia, and Brazil. The pandemic forced a moratorium on my dissertation data collection and required that I restructure my research study. At the end of my data collection before the national lockdown was implemented, my study completed data collection on 100 2G adults and 87 3G children. Consequently, I was unable to complete the initial study aims I initially sought out to complete. While COVID-19 drastically disrupted my research activities, let alone daily life, my team of dedicated research staff and I learned to adapt to these shifting conditions. In turn, we created new opportunities for taking care of ourselves, supporting our study participants, and conducting novel research. Thus for this dissertation, through a combination of primary and secondary data analysis on survey data from Soweto, I examine the

intergenerational impacts of prenatal and early life postnatal stress exposure on birth outcomes, adolescent psychiatric morbidity, and adult depressive risk across three separate samples of infants, children, and adults living in Soweto.

1.6 Dissertation outline

This dissertation is outlined into nine chapters. Chapter 2 illustrates the theoretical framework for this study. Chapter 3 describes the various samples and methods used in this dissertation. Chapters 4-6 present a series of quantitative data analyses on the impacts of prenatal and postnatal early life stress among families in Soweto. Chapter 4 examines the impact of maternal prenatal stress during the first trimester on infant birthweight in a birth cohort study conducted between 2013-2016. Chapter 5 explores the long-term mental health impacts of maternal prenatal stress experienced across pregnancy during the dissolution of apartheid (c. 1990) among late adolescents aged 17-18 years old. Chapter 6 evaluates the impacts of childhood trauma and perceived COVID-19 infection risk on depressive symptomatology in a community-based sample of adults in 2019-2020. Finally, Chapter 7 ummarizes my key findings and discusses the broader relevance and potential impacts of this research. I close with a summary of my dissertation and a discussion of future directions. Ultimately, findings from this biocultural investigation can help strengthen the public health of historically oppressed communities and assist societies overcome the lasting consequences of intergenerational trauma.

CHAPTER 2: Background and Theory

In this chapter, I describe the mechanisms that underlie the depressive impacts of intergenerational trauma and early life postnatal stress. I first discuss the global burden of mental illness and the disproportionate impact in historically traumatized and low- and middle-income contexts (Patel 2012; Vigo 2016). I then briefly introduce the idea that past traumas may manifest intergenerationally through stress-sensitive biological mechanisms to increase the risk of depression. Afterwards, I describe depression as a disease and its most well-known predictors. I then describe the biology of prenatal and postnatal early life stress, which I collectively refer to as "early stress," and adult depression. Later, I trace the various biological and developmental mechanisms involved in gestation, parturition, and hypothalamic-pituitary-adrenal (HPA) axis function – one of several physiological system known to regulate the vertebrate stress response. I then introduce the developmental origins of health and disease (DOHaD) framework (Barker 1999) as a lens into some of the biosocial mechanisms through which prenatal stress-initiated intergenerational trauma are understood to operate. I then describe how early stress impacts these processes to possibly increase depression risk later in life (Heim & Binder 2012; Karlamangla et al. 2019). This discussion of the major developmental theories and physiological mechanisms underlying the lifecourse biological impacts of prenatal stress exposure is key to highlight the current gaps in the scientific literature on the long-term impacts of prenatal stress on adult mental health (Barker 1999; Gluckman et al. 2010; Heim et al. 2019; O'Donnell & Meaney 2017). I draw upon recent theoretical developments on the intergenerational biological transmission of stress, inequality, and social adversity (Conching & Thayer 2019; Kuzawa & Sweet 2009; Vineis 2020) to test the hypothesis that alterations greater prenatal stress is associated with alterations in stress physiology, in particular the HPA axis function, which in turn correspond with increased

mental illness risk during adulthood (Goldstein et al. 2019; Heim et al. 2019; Krontira et al. 2020).

2.1 Introduction

Trauma, biology, and global mental health

Mental illnesses and substance use disorders account for the leading cause of disability worldwide based on the 2010 Global Burden of Disease study, accounting for 23% of all years lived with disability (Whiteford et al. 2013). Despite the major role of mental illness in shaping global patterns of morbidity, issues of mental health continue to be an underappreciated and underrecognized issue in global health (Ngui et al. 2010). These major health concerns drove a diverse set of stakeholders – including international health organizations, academics, and global health officials – to create a foundation for what would be the new field of "global mental health" (GMH)[2] (Patel 2012). Global mental health, as such, is defined as "an area of study, research, and practice that places a priority on improving [mental] health and achieving equity in [mental] health for all people worldwide." (Patel & Prince 2010:xi). GMH particularly prioritizes the diseases and issues based in "low- and middle-income countries" (World Bank 2020), where the burden of mental illness is estimated to be the greatest (Patel 2007; Vigo 2016) and where policies for mental health care and protections against individuals affected by mental disorders are least likely to exist (Ngui et al. 2010).

[2] The convergence of four trends produced the impetus for GMH to develop: greater evidence on the social determinants of mental health, the creation of the "disability-adjusted life year" as a metric, growing evidence on the cost-effectiveness of pharmacological and psychosocial treatments, and the widespread violence and death among individual with mental illnesses in societies across the world (Patel 2012).

South Africa has become a major site for GMH work in the African continent (WHO 2007). Major findings on the widespread prevalence and incidence of mental illness, as well as the massive treatment gaps in public mental health facilities, have brought international attention to the large disease burdens of mental illness in South Africa. Throughout the short yet dense history of global mental health research, understanding and addressing the widespread mental health impacts of psychosocial stress and trauma worldwide has become a primary focus in the field and across global health practice. This focus is particularly relevant to South Africa, where everyday violence, substance abuse-related complications, poverty and inequality, among other stressful and traumatic life events, are major risk factors for mental illness (Burns et al. 2011; Seedat et al. 2011). Since apartheid, South African society continues to be plagued by the persistent societal institutions of apartheid, including chronic poverty (Gibbs et al. 2018), discrimination (Williams et al. 2008), and racialized social inequality (Adjaye-Gbewonyo et al. 2016; Burns 2015), all of which are known risk factors for psychiatric disease (Allen et al. 2014; Moomal et a. 2009; Myer et al. 2008).

In addition to the psychological and psychiatric sequelae of stress, trauma, and inequality, growing research has highlighted the disproportionate impacts of early life childhood exposure to stress and trauma on psychopathological risk across the lifecourse (Mandelli et al. 2015; Raleva 2018). The developmental effects of early stress exposure are also known to affect later-life risk for a wide range of future phenotypic outcomes, including growth patterns, metabolic function, inflammatory profiles, and stress-regulatory neuroendocrine systems (Belsky 2019; Karlamangla et al. 2019; Nettis et al. 2019; Watamura & Roth 2019). The durable effects of early life psychosocial stress exposure are also known to predict adult depression beyond the influence of

genetic predispositions, as these patterns have been reported in twin studies (Kendler et al., 2000; Nelson et al., 2002).

2.2 Social and developmental determinants of adult depression

Adult depression: definitions, predictors, and epidemiology

Depression is the leading cause of disability worldwide (Friedrich 2017). Depression, also known as major depressive disorder (MDD) or clinical depression, is a mood disorder that is characterized by persistently sadness, low mood, and loss of interest, which can cause major impairments one's daily life (American Psychiatric Association 2013; South African Depression and Anxiety Group 2020). Symptoms of the condition vary across individuals, but the major characteristics of depression include depressed mood, diminished interest, weight change, slower thoughts and movements, fatigue, feelings of worthlessness, difficulty concentrating, and recurrent suicidal ideation (American Psychiatric Association 2013). Depression seen and experienced across the lifecourse, from childhood to late adulthood, and the incidence of depression increases dramatically during adolescence (Pine et al. 1998, 1999). And while depression is a common illness experience worldwide (Kleinman 1985), the disease is one that is not universally observed across cultures and has not always been seen throughout history (Kleinman et al. 1985, 2004; Watters 2010) – thus emphasizing the social, political, and cultural dimensions of the disease category (Kirmayer 2001).

Anxious, atypical, and melancholic symptom presentations have been used to classify subtypes of depression and categorize the heterogeneity of depression. Anxious depression is the co-occurrence of both depressive and anxious symptoms and understood to be a more severe form of MDD, characterized by greater depression severity, more suicidal ideation, worse

treatment outcomes, and poorer overall functioning (Häberling et al. 2019). Atypical subtypes are characterized by greater mood reactivity, two or more of the following features - increased cases of appetite, sleep, leaden paralysis, and interpersonal rejection sensitivity - for at least two weeks, and non-overlapping presentations with melancholic or catatonic features of depression (APA 2013). Melancholic depression is a form of MDD where the main indicator is prolonged anhedonia and/or poor mood reactivity supplemented with at least three of the following: depression independent of bereavement, decreased weight and appetite, psychomotor function, early waking, excessive guilt, and worse mood in the morning (APA 2013). The use of these subtypes, however, are controversial. Arnow and colleagues state that "data on the clinical utility of these subtypes in treatment selection—that is, whether particular subtypes show different patterns of symptom reduction with any given treatment—are inconsistent" (Arnow et al. 2015:743). Studies on disease prognosis, neuroanatomy, and treatment response suggest that the subtypes may be biologically distinct. For example, melancholic patients respond less effectively to antidepressant medications compared to those who aren't melancholic (Uher et al. 2011), yet findings are inconsistent (Bobo et al. 2011; Yang et al. 2013). Further research is necessary to determine the clinical, pathophysiological, and treatment differences in these current subtypes of depression (Arnow et al. 2015).

Similar to many physical and mental diseases, the primary determinants and etiology of depression are multifaceted, complex, and variable both within and between people (Goldberg 2011). The major predictors of depression include stress and trauma, gender, age, genetic and biological factors, personality type (e.g. neuroticism), substance use, major life events and transitions, comorbid diseases, and broader histories and experiences of oppression (Kleinman 2001; Patel et al. 2010; Peltzer & Pengpid 2020; Pine et al. 2002), though the vast variation at

the individual and population levels and the culturally-specific nature of depression highlights the fact that other determinants are at play (Assari 2017).

In South Africa, depression is considered a major public health concern by various stakeholders ranging from patients and caregivers to the national government and countrywide civil society groups (Docrat et al. 2019; Herman et al 2009; South African Depression and Anxiety Group 2020). National estimates of the epidemiology of adult depression are fairly recent - the first national representative figure was produced in 2009 (12-month prevalence: 4.9%, lifetime prevalence: 9.7%). These and other national prevalence estimates, however, have been widely criticized for reasons specific to measurement in the South African context and those also seen worldwide (e.g. underreporting of mental health data, poor instrument validity, cultural variation in disease experience, socioeconomic constraints, etc.) (Tomlinson et al. 2009). Other national-level estimates, regardless of representativeness, report variable findings. These include estimates from the National Income Dynamics Study, which reported 27.1% of respondents experienced "depressive symptoms" in 2012 and 13% in 2015-16, and a national prevalence rate of 4.6% in 2015 based on the World Health Organization. While current estimates predict that the prevalence rate ranges somewhere between 4-5%, rates in marginalized communities such as those experiencing poverty (Lund et al. 2010), disease morbidity (Remien et al. 2019), and violence (Herman et al. 2009) are elevated. Substantial evidence also shows that depression poses major deleterious impacts on quality of life, health, and well-being in South Africa (Herman et al. 2009; Remien et al. 2019; Tomlinson et al. 2009; South African Depression and Anxiety Group 2020).

Below I describe the major determinations of adult depression seen worldwide, many yet not all of which are potent risk factors in South Africa. These include stress and trauma, systems

of power (e.g. race, class, gender, etc.), and development. I first provide a brief historical overview of the concepts of stress and trauma and discuss the operational definition of both terms in this dissertation. I then describe how each of these predictors affect depression in adults.

Stress and trauma: conceptual histories and definitions

I. Stress

Stress and trauma are both polysemous terms that index various meanings within and across disciplines and also depending on the system in question (e.g. biology, individual, family, organization, community, environment, etc.). The earliest known use of the word stems from the 14th century to describe adversity, hardship, and affliction (Lumsden 1981). Various meanings and uses of the term emerged overtime and landed in medical texts of 19th century Western medicine, where it was understood as a basis of ill health and disease (Lazarus & Folkman 1984). Much of the origins of today's rich literature on stress and health derive from the work of two scientists – American physiologist, Walter Cannon (who also coined the term "fight or flight response") and Hungarian endocrinologist, Hans Selye. In his seminal book titled *The Wisdom of the Body,* Walter Cannon[3] (1932) conceptualized stress as a perturbation of disruption of homeostasis due to altered conditions internally, such as changes in hormone balances, physiological function, and nutritional status, etc., and externally, such as temperature, oxygen availability, environmental threats, etc. Also in the mid 1930s, Hans Selye deployed the "stress"

[3] Cannon also developed the long-standing ideas of homeostasis used today. This idea represented the processes of physiological regulation that maintained constancy, operated through the process of "steady-state" conditions (that any change will be met with resisting change), comprised of numerous biological mechanisms, and that intentionally occurred (rather than it being a chance process). Cannon extended French physiologist Claude Bernard's early work on cellular environments, in which he explained how cells and tissues in multicellular organisms protect themselves and respond to stress.

concept to mean a tightly regulated set of physiology responses to defend the body from both physical insult and psychological adversity (Lazarus & Folkman 1984) – a reaction he termed the General Adaptation Syndrome (Selye 1946).

In contrast to Cannon's operationalization of stress, which emphasized the external nature of the "stressor" that altered homeostasis, Selye's view of stress fully indexed what he perceived as the "unitary" physiological reaction and process created by the human body when faced with such demands (Fink 2010; Lazarus & Folkman 1984). These pioneering scholars laid ground for future groundbreaking work on stress and health from researchers like American psychologist Richard Lazarus, who viewed stress from the perspectives and dynamics of cognition; British epidemiologist David Barker and his ideas on the developmental effects of early life conditions; and John Newport Langley, the British physiologist who coined the term "autonomic nervous system," and American anthropologist Daniel Brown who contributed greatly to the study of stress and human adaptability and biocultural frameworks in anthropology. Since the seminal work briefly reviewed above, various conceptualizations and definitions of stress have emerged across disciplines. Selye and Lazarus both emphasize this trend, explaining the difficulties of reaching a consensus on the overarching definition of "stress":

> "In spite of consistent confusion about the precise meaning of the term, stress is widely recognized as a central problem in human life. Scientists of many disciplines have conceptualized stress but each field appears to have something different in mind concerning its meaning. For the sociologist, it is social disequilibrium, that is, disturbances in the social structure within which people live. Engineers conceive of stress as some external force which produces strain in the materials exposed to it. Physiologists

> deal with the physical stressors that include a wide range of stimulus conditions that are noxious to the body. In the history of psychological stress research, there has been no clear separation between physical stressors which attach biological tissue systems and psychological stressors which produce their effects purely because of their psychological significance" (Lazarus et al. 1962:26; Selye 1976:18).

When viewing existing concepts of stress together, the overarching theme across all perspectives view stress as "*a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease*" (Cohen et al. 1997, see Figure 1). The operational definition of stress in this dissertation will use this definition, with the caveat that the use of the term "adaptive" indexes the concept of psychological adaptation, which refers to "changes that take place in individuals or groups in response to environmental demands" (Berry 1976; Berry 1997:13), rather than the meaning from evolutionary biology that describes the process that fits organisms to their environment, resulting in grater fitness, as well as a trait that serves a functional role that is maintained and evolved over time due to natural selection.

The predominant framework used to understand the relationship between stress and depression is the stress-diathesis model (Monroe & Simons 1991; Zuckerman 1999). The stress-diathesis model suggests that individuals with greater vulnerability or predisposition – whether a difficult temperament, biological, endophenotypic, genetic, etc. – are more likely to respond negatively to an environmental stressor (Monroe & Simons 1991; Zuckerman 1999). The stressor can be a range of psychological exposures or external insults, including psychosocial stress, physical trauma, violence, etc. The original "diathesis-stress" conceptualization comes

from theories of schizophrenia during the 1960s (Bleuler 1963; Rosenthal 1963), which eventually was adopted by depression researchers (Bebbington 1987; Monroe & Simmons 1991; Robins & Block, 1989). The motivating idea of the original conceptualization - that stress interacts with a pre-existing diathesis, which in turn actualizes the potential of disease vulnerability into the presence of psychopathology (Monroe & Simmons 1991) – persisted to today's use of the model (Belsky & Pluess 2009).

Psychologists, biologists, and public health researchers have greatly expanded the stress-diathesis model by examining the various moderators, or a factor that affects the direction and/or strength of the relation between a predictor and dependent variable, and mediators, a variable involved in the mechanism of an observed relationship between a predictor and outcome, of the stress-depression relationship. These include biological, developmental, psychological, and social/cultural pathways. Biological factors include the role of stress physiological mechanisms, such as the HPA axis (Heim & Binder 2012), inflammation (Miller et al. 2011), biochemical mechanisms (Belujon & Grace 2017), neurobiological function (Teicher et al. 2016), epigenetics (Heim et al. 2019), and more recently, the microbiome-gut-brain axis (Cryan et al. 2019). Developmental perspectives emphasize the importance of childhood adversity (Heim & Binder 2012) and more recently prenatal stress (Monk et al. 2019), chronic stress (Hammen 2015), and developmental stress sensitization (Kendler et al. 2004; McLaughlin et al. 2010). Psychological pathways include examinations of cognition, personality traits, self-esteem, and attitudes (Hammen et al. 2015). And finally, social/cultural perspectives examine the types, meanings, and cultural relevance of stress and mental health, including studies of stigma, victimization, violence against women, and broader systems of oppression (Kim et al. 2020). These pathways

are frequently studied in tandem with each other to understand the various phenotypic outcomes and processes, including buffering, sensitization, gene-environment interactions, etc.

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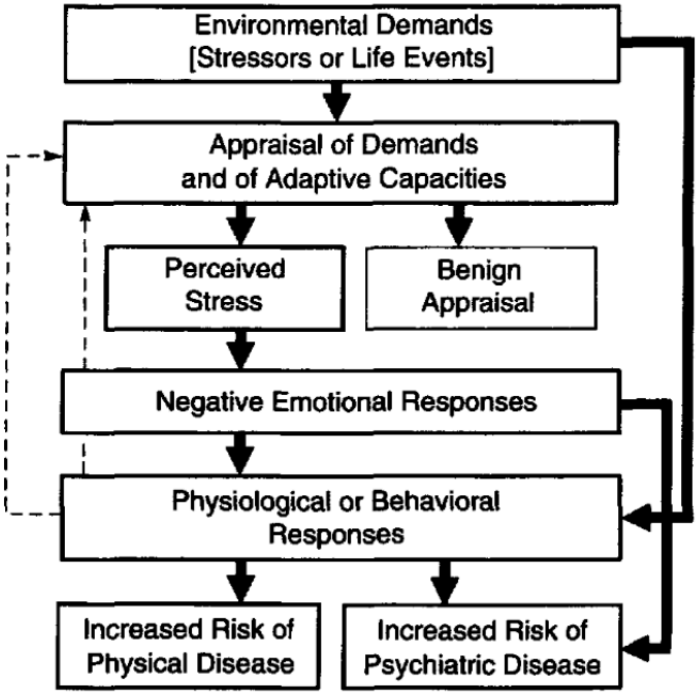


Figure 1.1 **A heuristic model of the stress process designed to illustrate the potential integration of the environmental, psychological, and biological approaches to stress measurement.**

Figure 1. Heuristic model of stress that incorporates environmental, psychological and biological processes in conceptualizing stress based on the work of Cohen, Kessler, and Gordan (1997).

II. Trauma

Decades of research in psychology, social work, and other allied fields have documented the well-known pathological outcomes of traumatic experience. Mental health practitioners have responded accordingly, by developing and optimizing best practices for addressing and

preventing the wide-ranging sequelae of trauma. In psychology and psychiatry, trauma is broadly defined as an event outside the range of usual human experience that disturbed the psyche's normal capacity for homeostasis and coping (Fassin & Rechtman 2009). Among the most well-known definitions of trauma comes from Dutch American psychiatrist Bessel van der Kolk, who defines trauma as "the impact of experiences that overwhelm both psychological and biological coping mechanisms" (Van der Kolk 1987:xii) and its effects include the "emotional and cognitive processes, underlying biological changes, and resulting psychopathology" (Van der Kolk 1987:xii).

In their book *The Empire of Trauma,* Fassin & Rechtman (2009), a team of prominent French physician-anthropologists, dissect the medical theory and social history of psychological trauma. Examining the genealogy of the concept between the late 1800s to 1980, the authors closely examine the "dual genealogies" of trauma: one of academic perspectives from psychiatry, psychology, and psychoanalysis, and the other in personal "collective sensibilities," morals, and values. The psychic dimensions of trauma sequelae, they argue, originated from early discussions in psychology and psychiatry that sought to subsume the neurological effects of railway accidents, also known as "trauma neurosis," into the larger diagnosis of hysteria. Existing psychic theories of hysteria, developed by leading psychologists Pierre Janet and Sigmund Freud, subsequently incorporated "trauma neurosis, as well as the etiological "event," into its explanatory models. This eventually gave rise to a Freudian understanding that directly implicated the external "traumatic" event with internal origins of psychologized trauma sequelae. This conceptualization of trauma-based injuries co-emerged with the rise of legislation around occupational safety and workers compensation, which is the moral dimensions of trauma first emerge and play out in larger society.

Manual laborers and soldiers during World War I who developed trauma neurosis as a result of workplace accidents or combat, respectively, deeply scrutinized because of the moral judgements of others that assumed feigned injury for financial compensation or malingering. In fact, among military personnel, trauma neurosis was "recast as the selfish desire, whether conscious or unconscious, to escape fire" and "came to occupy center stage in the theatre of disgrace" (Fassin & Rechtman 2009:43). It took the occurrence and examination of Nazi extermination and concentration camps that ultimately led to the end of an "era of suspicion," or the hegemonic, morally-charged skepticism of trauma sequelae. In turn, the impacts of trauma became reconfigured from a subject of moral scrutiny into undeniable evidence of ethical suffering, which mediated the emergence and the social positioning of post-traumatic stress disorder. Here we see the "shift from one truth to another, from a realm in which trauma was regarded with suspicion to a realm in which it carries the stamp of authenticity" (Fassin & Rechtman 2009:23).

Afterwards, the introduction of post-traumatic stress disorder (PTSD) as a new American psychiatric concept to explain the collection of psychological and somatic sequelae of war trauma among Vietnam veterans both affirmed and transformed the concept of trauma. First, the new disease category of PTSD concretized the perspective that trauma survivors experienced "ethical suffering," in turn depoliticizing the reason and context for the traumatic event. Second, trauma entered deeper into the biomedical world and eventually became incorporated into clinical theory, biological frameworks, and diagnostic practice, which is the conceptual framework of trauma we see today in Western psychiatry and most of global mental health. I use Van der Kolk's definition above as the operational definition of trauma for this dissertation: "the impact of experiences that overwhelm both psychological and biological coping mechanisms"

(Van der Kolk 1987:xii) – with the additional caveat that both the stressors and traumas are deeply tied to the political and intentional systems of white supremacy from which the traumas I examine in this dissertation derive (Barbarin & Richter 2001).

Intersectional systems of oppression and health: social identity, inequality, and power

I. Intersectionality

A strong and longstanding literature on the social determinants of adult depression has explored the role of race, class, gender, and other social dynamics in the risk and experience of adult depression. While anthropological, psychological, and other social science research fields have examined each of these dimensions of social identity, inequality, and power as a distinct social dimension (e.g. race, class, gender, etc.), a strong theoretical framework informed by the history and lived experiences of communities of color has emerged to understand social systems of power and inequality, a concept known as intersectionality.

Critical race theorist and legal scholar Kimberlé Crenshaw (1990) coined the term "intersectionality" in the last 1980s to early 1990s to describe the "multidimensionality" of marginalized people's lived experience (Crenshaw 1989:139) and actively reject the "single-axis framework" of examining singular social dynamics (e.g. race, class, gender, ability, etc.) to understand oppression - and in the case for Crenshaw's pioneering work, to analyze the numerous way that race and gender shape the power, oppression, and experiences of Black women. (Crenshaw 1989, 1990). This core concept in critical race studies and anti-racist organizing derived from Crenshaw's legal scholarship, which aimed "to [problematize] law's purported colour-blindness, neutrality, and objectivity" (Cole 2008). Furthermore, intersectionality intentionally rejected harmful social theories and flawed legal practices,

including the perpetuation of identity politics as an analytical framework, which fails to provide theoretical and analytical spaces for understanding intra-group differences in power and oppression (e.g. racialized experiences of womanhood, classed and gendered experiences of being Asian American, etc.) (Crenshaw 1992).

II. Mental healthcare access and treatment

Medical anthropologists adopted Crenshaw's theory of intersectionality and produced foundational scholarship on the intersectional perspectives of health and well-being. In particular, medical anthropologist Leith Mullings, a Black woman and professor at the CUNY Graduate Center, wrote extensively on the intersecting dynamics of gender, race, and class to display how healthcare is differentially accessed and experienced. Similarly, mental health disparities are also produced and sustained through intersectional processes.

In South Africa, poor access and poor quality mental healthcare is a major system by which intersectional forms of oppression deleteriously impact mental health and raise risk for depression. In South Africa, the people who need greatest need of mental health services are least likely to get them (Docrat et al. 2019), which typically include low-income individuals of color – including Black, Coloured, and Indian racial groups – and identical groups from immigrant backgrounds, such as Zimbabweans, the Basotho, Mozambicans, etc. (Das-Munshi et al. 2016; Vearey & Núñez Carrasco 2010; Williams et al. 2008). There is very low availability and access to a public psychiatrist, particularly in rural areas, which are overwhelmingly Black, low-income, and lacks other forms of medical care. For example, there is an average 0.31 public sector psychiatrists per 100 000 uninsured population in the country (Docrat et al. 2019).

Unsurprisingly, poor access to healthcare facilities due to distance, functional impairment, discrimination, and disease morbidity is a major predictor of depression risk (Peltzer & Phaswana-Mafuya 2012; Rochat et al. 2006; Tomita et al. 2017). Furthermore, the opposite is also true – greater depression and poorer mental health is associated with poorer healthcare seeking behaviors and clinic attendance (Nwakasi et al. 2020; Ramirez-Avila et al. 2012), which could exacerbate the state and prognosis of current conditions, most commonly HIV, TB, and diabetes (Kagee et al. 2010; Nyirenda et al. 2013; Petersen et al. 2014; Simbayi et al 2007). Here we see that intersectional oppressive forces of racism, geographic segregation, gender-based violence, and classism, and other social conditions depending on context, dynamically combine together to stratify risk of, access to, and resources for preventing and treating mental illness.

In addition to these intersectional dynamics that produce mental health disparities, the public mental healthcare infrastructure and national mental health policies in South Africa are also severely limited, which in turn compromise access to healthcare and threaten mental health. An ambitious and comprehensive mental health policy was written and published in 2014 aimed at addressing many of the country's prevalent and burdensome mental health issues, but the national mental healthcare policy was never funded nor implemented (Docrat et al. 2019). Limited healthcare infrastructure also creates conditions for chronic medication stockouts and staff shortages (Docrat et al. 2019), which also limits the number of student psychologists that clinical training programs can accept and place in South Africa.

Stress, trauma, and depression: intersectional perspectives on a major predictor of depression

Like trends seen in the broader literature (Carr et al. 2013; Paykel 1976; Turner & Lloyd 1995), mental health, and depressive specifically, in South Africa is greatly exacerbated by

increasing durations and severities of psychosocial stress and trauma (Kaminer et al. 2008; Kaminer & Eagle 2010; Manyema et al. 2018; Williams et al. 2007; Williams et al. 2008). Intersectional systems of oppression structure, enforce, perpetuate, and protect against the these deleterious impacts on health and well-being as well as the ability to successfully overcome adversity and maintain positive health in South Africa and in afflicted communities across the world (Bauer 2014; Crenshaw 1999; Evans 2019; Kim et al. 2019; Moodley 2019; Mullings 2014; Schulz & Mullings 2006; Viruell-Fuentes et al. 2012). The modes through which stress and trauma have politically distributed effects on depression and mental health include a wide variety of widely-studied social determinants of health. The political project of apartheid, social technology of "race," and its widespread management of society both intricately and efficiently structured societal violence along similar multidimensional dynamics that intersectionality models, particularly because apartheid and its effects were designed based on politics of identity (e.g. "race," class, migration status, gender, etc.) (Beinhart 2001). These legacies of intersectional oppression strongly persist today (Francis 2019; Klasen & Minasyan 2020; Moodley 2019). Intersectional experiences of poverty, gender- and sexual-based violence, everyday violence, and disease are among the most potent and common pathways through which stress and trauma are faced.

Structured by the strict identity politics of apartheid, the distribution and impacts of stress on mental health are intersectionally distributed in ways that have greatest adverse effects on those who resist more systems of oppression at the same time and have resisted these systems historically (e.g. racism, classism, xenophobia, disability, homo-/transphobia, etc.). Conversely, those who benefit from holding multiple power-holding social positions (e.g. whiteness, patriarchy, able-bodied, citizenship, wealth, etc.) are shielded from and are able to weather future

adversities and maintain good health. For example, in a study of Black cancer patients in Soweto, I found that male prostate cancer patients who were more likely to have a positive prognosis were sustained by their physical ability to work and generate income (e.g. ability and wealth), received adequate familial support and exercise patriarchal roles to request assistant (e.g. social capital, gender), and who were South African citizens rather than immigrants (e.g. those from Lesotho, Swaziland, Zimbabwe, etc.) – yet still experienced various forms of racial violence and economic marginalization as Black African men.

I. Poverty

Poverty is a major determinant of mental illness worldwide, including in South Africa (Kagee et al. 2010; Lund et al. 2010; Nyirenda et al. 2013). A variety of conditions ranging in severity, frequency, and time increase an adult's risk of depression. These include but are not limited to, conditions of psychological stress (Mungai & Bayat 2019), food insecurity (Tomita et al. 2019), financial strain (Turbeville et al. 2019), poor healthcare access (Docrat et al. 2019), unemployment (Elwell-Sutton et al. 2019), elevated disease risk and morbidity (Kim et al. 2020), racial discrimination and societal inequality (Williams et al. 2008), and histories of sustained adversity (McIsaac 2019). All of these conditions have been operationalized as forms of acute and chronic psychosocial stress, trauma, and/or social adversity and depending on the nature of the exact stressor, can have distinct effects on raising depressive risk, such as the case of limited healthcare access in preventing treatment of a comorbidity that may exacerbate depressive symptoms if not treated (e.g. HIV, TB, diabetes, etc.). Furthermore, these conditions of intersectional oppression disproportionately affect low-income, Black, migrant, queer, non-binary, and disabled individuals (Moodley 2019; Moreau 2015).

II. Violence

Crime and everyday violence have long been perceived as prevalent conditions in South Africa (Butchart et al. 2000; Louw 1997; Richter et al. 2018; Van Niekerk et al. 2017) and are major risk factors for depression in the country (Hartley et al. 2011; Jewkes et al.; Martinez et al. 2002; Peltzer & Pengpid 2013; Womersley et al. 2017). Intimate partner, gender-based, and sexual violence are major issues that disproportionately impact girls and women (Gass et al. 2010; Gibbs et al. 2018; Jewkes et al. 2010; Peltzer & Pengpid 2013), yet the impacts on other genders and sexualities are also major public health concerns. In particular, sexual violence also affect boys (sometimes at higher rates), men, and other non-binary genders and non-heteronormative sexualities (Madu & Peltzer 2000; Meinck et al. 2017). Yet the lack of awareness and research on their experiences as well as the gendered stigma against victimhood limits the support of these communities (Madu & Peltzer 2000; Meinck et al. 2017). South African artist Zanele Muholi writs poignantly of the multi-layered forms of oppression that structure of lives of Black African lesbian-identifying people and highlights how various dimensions of racism, homophobia, misogynoir, citizenship, and nationalism affect subjectivity: "The reality of being black and lesbian in South Africa is that we become 'outsiders' inside our townships or rural communities because there are those who have defined homosexuality in racial and ethnic terms as 'un-African'" (Muholi 2004:118-19).

III. Disease

The extended and multilayered histories of disease epidemics in South Africa pose numerous threats to mental health, and multiple studies report the depressive impacts of disease

risk and morbidity (Bosire et al. 2020; Kagee et al. 2010; Kaminer et al. 2008; Kim et al. 2019; Nyirenda et al. 2013; Petersen et al. 2014; Simbayi et al 2007). States of morbidity, comorbidity, and multimorbidity with conditions common in South Africa, including HIV, TB, hypertension, diabetes, and other chronic diseases, are major risk factors for depressive mood and MDD (Kaminer et al. 2008; Kim et al. 2020; Nyirenda et al. 2013; Petersen et al. 2014; Simbayi et al 2007). This relationship is understood to operate through a multitude of pathways – stress and other social experiences like disclosure, stigma, and illness experience (Bantjes et al. 2016; Kim et al. 2020; Tomlinson et al. 2009), biological interactions that increase depressive risk such as HPA axis dysregulation (Ramkisson et al. 2016) and neuroinflammation from infectious disease like HIV, TB, and syphilis (Rivera-Rivera et al. 2016; Spies et al. 2018), the economic impacts of morbidity (Lachman et al. 2014; Lund & Cois 2018).

IV. Positive mental health

South African families commonly experience multiple, intersecting forms of stress, trauma, and violence simultaneously and also draw from various sources of support – personal, interpersonal, family, community, religious, political – to continue daily living, maintain health and well-being, and thrive (Kim et al. 2019). A variety of positive resources and experiences have been documented to improve depression and health outcomes, including psychological resources (Somhlaba & Wait 2009), strong ethnic identity and belonging (Hocoy 1998; Norris et al. 2008), access to medical care (Kim et al. 2019), family and social support (Casale et al. 2015; Kim et al. 2019), and religion (Copeland-Linder 2006; Kim et al. 2019). These resources and experiences are understood to lead to positive mental health outcomes due to the health-buffering, -protective, and/or -promotive impacts on the individual.

The vast pluralistic landscape in South Africa is home to a multitude of African and international cultures, thus necessitating a similar medical pluralistic landscape. Traditional medical practice and therapeutic harmony between traditional ways of healing and biomedicine are important factors in maintaining health, particularly among non-White communities in South Africa (Burns & Tomita 2015; Campbell-Hall et al. 2010; Sorsdahl et al. 2009). For example, psychiatric presentations in many African communities in the country and across the continent are often seen to have various etiologies, including psychological and biomedical origins as well as cultural, spiritual, and religious reasons, such as ancestral communication, generational social debt and guilt, bewitchment, callings for becoming a spiritual healer (*intwaso*), and others (Egbe et al. 2014; Strumpher et al. 2014). Ancestral, spiritual, and religious systems have massively important influence across many communities in South Africa, regardless of race, class, gender, and geography (Kim et al. 2019; Núñez Carrasco 2015; Palmary et al. 2014). Finally, psychological services, such as counselling (Petersen et al. 2012a), public mental healthcare (Marais & Petersen 2015; Lund et al. 2008), and health systems strengthening methods such as task-sharing (Lund et al. 2020; Petersen et al. 2012b) have all produced deeply therapeutic or promising impacts on the mental health and well-being of families in South Africa.

Early development: childhood and prenatal exposures

There is substantial evidence that shows that postnatal early life stress is a major risk factor for depression during adulthood (Heim et al. 2012; Mandelli et al. 2015; Miller et al. 2011; Taylor et al. 2011). Overall, the literature on early life stress convincingly and consistently shows that histories of childhood stress and trauma elevate individual risk of developing depression during adulthood (Carr et al. 2013; Heim & Binder 2012; Hovens et al. 2010;

Mandelli et al. 2015; Wiersma et al. 2009) and a wide range of other adult health outcomes. For instance, individuals with histories of childhood trauma and chronic stress across development exhibit increased behavioral stress reactivity (Oosterman et al. 2019), heightened cortisol reactivity (Heim et al. 2019), and elevated inflammatory profiles (Müller et al., 2019) in response to future stressors.

Much of the work on early life stress and later depressive risk comes from studies of retrospectively reported experiences of childhood trauma (Bremner et al. 1993; Glaser 2000; Heim & Binder 2012). A seminal study of health insurance patients at Kaiser Permanente in the United States greatly advanced medical and public health research on early life stress. This study showed that past experiences of "adverse childhood experiences" (ACES) strongly predicted a wide range of high mortality risk chronic diseases in adulthood (Anda et al. 1999; Felitti et al. 1998), including adult depression (Chapman et al. 2004). From this literature emerged recent pioneering research on the role of childhood trauma on neurobiology and psychiatric disease risk across the lifecourse into adulthood (Heim & Nemeroff 2001), including stress physiological mechanisms (such as the HPA and SAM axes, inflammation, and neurobiology) and adult depression.

South African research on the early life stress effects on adult depression and biology is rapidly growing. Cross-sectional and longitudinal research has supported the hypothesis that greater early life adversity will predict greater adult depressive risk (Kim et al. 2020; Manyema et al. 2018; Sabet et al. 2009; Seedat et al. 2009; Spies et al. 2018) and adverse biological outcomes, including altered neuroendocrine activity (Seedat et al. 2003; Fearon et al. 2017; Womersley et al. 2018), greater inflammatory profiles (Ngwepe 2017; Said-Mohamed et al.

2019), and elevated disease risk (Kagura et al. 2016; McGowan & Norris 2020; Munthali et al. 2016; Munthali et al. 2017; Naidoo et al. 2019).

The overall research patterns seen in human studies of prenatal stress and intergenerational outcomes follow similar trends to those that have accumulated in animal studies (O'Donnell & Meaney 2017; Monk et al. 2019). Across the human literature, the existing literature shows that greater severity of maternal stress during pregnancy generally is associated and worse mental health outcomes in the next generation, specifically between infancy to late adolescence (Buffa et al. 2018; Graignic-Philippe et al. 2014; Heim et al. 2019; Huizink & De Rooij 2018; Karlamangla et al. 2019; McGowan & Matthews 2018; Monk et al. 2019; O'Donnell & Meaney 2017). These outcomes among infants and children include attention deficit hyperactivity disorder (Rice et al. 2010), conduct disorders (MacKinnon et al. 2018), and internalizing disorders like anxiety and depression in adolescents (O'Donnell et al. 2014; Sharp et al. 2015). Studies on the long-term psychological and biological effects of prenatal stress, however, become severely limited as participants become older, especially after young adulthood (e.g. 18 years and older) and are mostly conducted in Western countries. Among these studies, the long-term effects of prenatal stress that have been documented among adults include major depression (Betts et al. 2015; DeSantis et al. 2015), anxiety (Betts et al. 2015), and suicidal behavior (Raleva 2018). A more detailed review of the long-term depressive and biological impacts of prenatal stress is presented later in this chapter.

What is not well known are biological, developmental, and psychological pathways by which early stress increases risk for depression during adult. Based on the current literature, greater severity of childhood trauma is hypothesized to cause durable increases in psychological and physiological stress reactivity into adulthood and increase one's risk of developing MDD

(Kendler et al. 2004; McLaughlin et al. 2010) – also known as the "stress sensitization hypothesis." A growing literature has documented that greater experiences of childhood trauma can alter the development of key stress physiological mechanisms, such as the HPA axis, immune system, and brain function, and potentially increase both behavioral and physiological reactivity to future stressors (Heim et al., 2019; Müller et al., 2019; Oosterman, Schuengel, Forrer, & De Moor, 2019). Recent evidence has also reported the long-term impacts of childhood maltreatment on brain regions such as the amygdala (Dannlowski et al., 2012) and hippocampus (Opel et al., 2014), which regulate the perceptions of threat appraisal and emotions (e.g. fear, sadness) and are involved in the pathogenesis of MDD (Teicher et al. 2016). These early life stress-linked alterations in stress physiology may subsequently predispose individuals to developing a suite of psychopathologies, including depression. In the following section, I will describe these major biological mechanisms known to underlie the etiology and course of adult depression as a result of early stress exposure.

2.3 The biology of early stress and depression: endocrine, neuroinflammatory, biochemical, genetic, and structural mechanisms

Despite the high prevalence and debilitating burden of depression worldwide (Patel 2010; Vigo 2016), the pathophysiology of depression lacks clear consensus (Krishnan & Nestler 2010). Growing evidence shows that childhood adversity, and potentially prenatal stress, increase one's risk of developing a variety of physical and psychiatric diseases, including depression (Baumeister et al. 2016; Danese & Lewis 2017; Miller et al. 2011; Murphy et al. 2017; Kelishadi & Poursafa 2014; Taylor et al. 2011). The underlying biological pathways that facilitate the long-term effects of early stress on adult depression, however, are still under investigation (Heim et al.

2019). In this section, I present the most understood biological mechanisms of early stress and adult depression in humans with the acknowledgement that this is not a comprehensive and detailed explanation of the vast and transient literature on the biology of adult depression. I describe five major biological pathways of adult depression from five distinct yet interrelated systems: endocrine, neuroinflammatory, biochemical, genetic, and structural mechanisms. This review takes special attention to the etiological pathways of stress. Additional pathophysiological mechanisms of depression are listed in Figure 2.

Endocrine pathways: the hypothalamic-pituitary-adrenal axis

Early life postnatal stress is a well-known predictor of altered adult HPA axis function (Butler et al. 2017; Fogelman & Canli 2018; Schalinksi et al. 2015; Trickett et al. 2010; van der Vegt et al. 2009). Early life stress is a strong risk factor for altered HPA axis function, which is characterized by flatter diurnal cortisol rhythms and altered cortisol reactivity to stressful events (Gustafsson et al. 2010; Heim & Binder 2012; Taylor et al. 2011; Thayer et al. 2018), though the direction of these relationships has varied across the literature. For example, early life stress is linked to both higher (Luecken & Appelhans 2006; Schalinski et al. 2015; van der Vegt et al. 2009) and lower levels of basal cortisol (DeSantis et al. 2015; Trickett et al. 2010; van der Vegt et al. 2009) during adulthood. Early life stress is also related to an altered cortisol awakening response (Butler et al. 2017; Engert et al. 2011; Fogelman & Canli 2018; Gonzalez et al. 2009) and evening cortisol levels (Engert et al. 2011; Gustafsson et al. 2010) in adulthood in both positive and negative directions. Additionally, adults with a history of child abuse and neglect exhibit altered HPA axis function as evidenced by elevated (Heim et al. 2000; Luecken & Appelhans 2006; Pesonen et al. 2010; Vaccarino et al. 2015) and blunted levels (Cărnuţă et al.

2015; Carpenter et al. 2007; Carpenter et al. 2011; Elzinga et al. 2008; Janusek et al. 2017; Lovallo et al. 2012) of cortisol reactivity in response to acute, laboratory-based psychosocial stressors.

Altered circadian HPA axis rhythms and HPA axis reactively has consistently been characterized as a neuroendocrinological phenotype of depression in animal and human studies (Adam et al. 2010; Doane et al. 2013; Heim & Binder 2012; Jarcho et al. 2013; Mangold et al. 2011; Vrshek-Schallhorn et al. 2013). Depressed patients and high depression risk adults have exhibited altered levels of bedtime cortisol and cortisol awakening responses (CAR) (Adam et al. 2017; Engert et al. 2011; Pruessner et al. 2003). For instance, higher bedtime cortisol has been reported to be characteristic of depression in both adolescents (Angold 2003; Dahl et al. 1991; Goodyer et al. 1996) and adults (Gold et al. 1988; Plotsky et al. 1998; Young et al. 1994). Similarly, higher CAR levels have been identified as a prospective risk factor for future MDD (Adam et al. 2010).

Based on current evidence, early stress-induced changes in HPA axis function subsequently may alter the output of key stress regulatory hormones, such as corticosteroids (e.g. glucocorticoids and mineralocorticoids) and catecholamines (e.g. epinephrine, norepinephrine, and dopamine). The effects of early stress on a collection of stress physiological mechanisms, including the HPA axis, are hypothesized to lead to the development of a vulnerable phenotype that causes adults to have an increased sensitivity to future stress, which in turn, elevates their risk for a range of mental illnesses (Heim & Binder 2012). These lasting effects of early stress on stress regulatory mechanisms like the HPA axis closely reflect key neuroendocrine features of adult depression. For example, in one study of adults living in metro Atlanta, adults with histories of child abuse exhibited patterns of HPA axis hyperactivity that mirrored similar

neuroendocrine, inflammatory, neuroanatomical, and behavioral patterns to those of depressed individuals (Heim et al. 2008; Heim & Binder 2012). Although not all depressed patients display HPA axis dysregulation (Heim et al. 2008), alterations in cortisol activity are thought to influence depression, possibly as a result of inflammation caused by glucocorticoid receptor insensitivity (Miller et al. 2009) and impairment of glucocorticoid-mediated negative feedback processes of the HPA axis (Pariante & Lightman 2008).

Neuroinflammatory and microbial pathways

Inflammatory processes have strongly been implicated in influencing the development of depressive symptoms (Danzter et al. 2008; Miller & Raison 2016) through a variety of pathways related to psychosocial stress and the inflammasome, micro- and astroglial activation in several brain regions, cytokine modulation of neurotransmitter levels, altered neurocircuitry (Miller & Raison 2016). Growing evidence has found that chronic and early life stress may elevate circulating inflammatory (Danzter et al. 2008; Miller et al. 2011), possibly due to greater HPA axis resistance and alterations in the inflammatory-regulating role of cortisol and also stress-initiated changes in metabolic function, which has shown to activate central and peripheral macrophages (Leonard & Myint 2009). Additionally, research has shown that chronic stress-induced hypercortisolism and inflammation initiates a cascade of molecular changes that alter the function of the serotonergic system, specifically the downregulation of serotonin turnover, which is a major endophenotype of depression and anxiety (Leonard & Song 1999; Leonard 2001). Some evidence suggests that adult depressed patients exhibit elevations in pro-inflammatory factors and decrease in anti-inflammatory factors (Myint et al. 2005; Leonard & Myint 2009).

The relationships between stress, inflammation, and depression, however, are still relatively unknown and a ripe area of biobehavioral and depression research.

Evolutionary perspectives also suggest that the lack of minimally infectious, tolerogenic microbiomes buffered an adaptive inflammation bias necessary for rapid pathogen defense and corresponding depressive symptoms that promoted healing (Rook & Lowry 2008). Early ancestral environments hosted a diverse world of microorganisms and parasites, and evolutionary pressures derived from a human co-evolution with these pathogens, in addition to predators and other conspecifics. Consequently, humans are believed to have developed both a heightened immunological response that was kept in balance by exposure to minimally pathogenic, tolerogenic microbes (i.e. “old friends) that suppressed inflammatory responses to allow tolerance of these “old friends” and secrete anti-inflammatory cytokines (i.e. IL-10, TGF-β) (Rook & Lowry 2008; Raison & Miller 2013). Empirical models and clinical trials that test the effects of “old friends” microbial exposure have shown promising treatments against allergies (Okada et al. 2010), autoimmunity (Janssen et al. 2016), and intestinal inflammation (Ramanan et al. 2016). Additionally, the gut microbiome is known to have a crucial role in the development and functionality of innate and adaptive immune responses (Round et al. 2010). The physical and psychological symptoms elicited by pro-inflammatory cytokines when presented in high levels also have considerable overlap with the characteristic symptoms of depression. These include low mood, changes in sleep and diet, decreased libido, and decreased social interactions (Leonard & Myint 2009).

Biochemical pathways: the monoamine hypothesis

The monoamine hypothesis represents the predominant biological theory of depression in psychiatry and medicine (Belmaker & Agam 2008; Boku et al. 2017; Cosci & Chouinard 2019; Jesulola et al. 2018; Liu et al. 2017). The hypothesis posits that "the reduced availability of these major monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) results in decreased neurotransmission and impaired cognitive performance which may lead to depression" (Jesulola et al. 2018:82). Evidence for this hypothesis emerged after studies found that inhibitors of the enzyme monoamine oxidase, catabolizes norepinephrine and serotonin – two well-studied monoamine neurotransmitters in mammals – in the presynaptic neuron before neurotransmission, corresponded with antidepressant outcomes (Belmaker & Agam 2008).

The monoamines that are currently understood to contribute to the etiology of depression include norepinephrine (both a stress regulatory hormone for the autonomic nervous system and a neurotransmitter known to modulate prefrontal cortex function, the processing of short-term and emotionally-stimulating memories, and behavior and attention (Maletic et al. 2017), serotonin (the largest cohesive neurotransmitter network in the brain that has wide ranging modulatory effects, including mood, cognition, learning, reward, memory, and many physiological functions around the body), and dopamine (involved in the modulation of reward, motivation, memory, and attention) (Delgardo & Morena 2006). Given their relevant roles in influencing the major symptoms of depression, these monoaminergic systems have become instrumental in elucidating the pathophysiology of depressive symptoms including fatigue, low mood, low interest and motivation, and psychomotor alterations (Delgardo & Morena 2006; Jesulola et al. 2018; Maletic et al. 2017).

The functional impairments of monoamine depletion operate through the catabolic effects of monoamine oxidases in the synaptic cleft, which results in a lowering of available monoamine neurotransmitters and decreased neurotransmission characteristic of depression (Belmaker & Agam 2008; Nemeroff 2008). This mechanism provides the basis for the use of monoamine oxidase inhibitors in antidepressants, as a method to replenish available monoamine concentrations (Coppen 1967). Additionally, more recent evidence suggests that characteristically greater stress reactivity among depressed individuals may encourage certain neurotransmitters, including histamine, glutamate, and norepinephrine) to interact and decrease the production of serotonin (Strawbridge et al. 2017). Other molecular pathways involved in decreasing the efficacy of monoamine pathways include decreased protein transport function (involved in facilitating the presynaptic reuptake of neurotransmitters) and altered receptor sensitivity on pre/post-synaptic neurons (Jesulola et al. 2018).

Recently in the past two decades, scientists have challenged the monoamine hypothesis after consistently noting several shortcomings of the framework. Three major criticisms have emerged (Liu et al. 2017):

1) The rapid rise of serotonin concentration in the synaptic cleft is inconsistent with the clinical delayed onset of antidepressant efficacy'
2) Reducing serotonin levels in synaptic cleft through tryptophan depletion or protein transporter enhancers did not induce depression in healthy adults, which was contrary to the monoamine depletion seen in depression.
3) Individuals with the *l* allele of 5-HTTLPR, coding for greater serotonin transport proteins and in turn, greater reuptake of synaptic serotonin, have exhibited reduced

risk of depression or better prognosis than allelic variants associated with decreased protein transport activity (*s* allele).

Additionally, as argued by leading American neuroscientists: “there is little evidence to implicate true deficits in serotonergic, noradrenergic, or dopaminergic neurotransmission in the pathophysiology of depression. This is not surprising, as there is no *a priori* reason that the mechanism of action of a treatment is the opposite of disease pathophysiology” (Krishnan & Nestler 2010:3). Building off of these criticisms, scientists have proposed new theories to explain the pathophysiology of depression. This includes the neuroplasticity hypothesis and the neurogenesis hypothesis of MDD, both of which explain decrease in hippocampal volume (Boku et al. 2017; Liu et al. 2017). Briefly, neuroplasticity hypothesis explains how brain morphological alterations due to shortening of dendrites and decreased density of dendritic spines shrink the hippocampus and alters function. And the neurogenesis hypothesis posits that lower neurogenesis in the dentate gyrus lowers hippocampal volume (Boku et al. 2017).

Decreased hippocampal volume is a key characteristic of MDD and the hippocampus is integral in regulating the negative feedback loop of the HPA axis. Adults who exhibit greater cortisol concentrations, due to chronic stress or because of a cortisol-elevating disease like Cushing’s syndrome, tend to exhibit smaller hippocampal volume. Ablations of the dorsal hippocampus or lateral fornix (the conduit of communication from hippocampus to the hypothalamus) have also shown to alter diurnal cortisol rhythms and elevate basal concentrations. In sum, a tight relationship between stress, the hippocampus, and HPA axis may trigger a negative neuroendocrine spiral that may underlie the pathophysiology of MDD and introduce new theories of the biology of depression.

Genetic and epigenetic pathways

Intergenerational studies of depression report heritability estimates of approximately 30-40% (Kendler et al. 2006; Wray & Gottesman 2012). Candidate gene analyses have strongly implicated single nucleotide polymorphisms (SNPs) in target genes. While numerous sites are known contributors of depression (Kendler et al. 2006; Krishnan & Nestler 2010), two genes have been repeatedly implicated in the genetics of adult depression – 1) *GNB3* (guanine nucleotide-binding protein-3) – coding for modulators and transducers in various transmembrane signaling systems (Yang et al. 2013) – and 2) *MTHFR* (methylene tetrahydrofolate reductase) (Shyn et al. 2010 – involved in the production of enzymes that allow for the reaction that produce methyl groups involved in loci-specific and global epigenetic activity (Wan et al. 2018). Genome-wide association studies (GWAS) have identified novel molecules [e.g. piccolo (a presynaptic nerve terminal protein), GRM7 (metabotropic glutamate receptor-7), etc.] (Krishnan & Nestler 2010), yet the statistical flaws and poor replicability of GWAS methodologies pose major caveats to the validity of these results (Meaney 2010).

Research on adults with histories of childhood stress and trauma has reported altered patterns of DNA methylation in genes that are involved in regulating the function and sensitivity of neural development, neurotransmission, neuroendocrine stress response systems, including the HPA and SAM axes (Albert & Benkelfat 2013; Cecil et al. 2020; Heim & Binder 2012; Kinnally et al. 2011; Korosi et al. 2012; Mehta et al. 2013; Raabe & Spengler 2013). The long-term depressive effects of early life stress have been understood to be facilitated by epigenetic regulation of downstream biological pathways involved in the pathophysiology of adult depression (Heim & Binder 2012; Park et al. 2019; Smith et al. 2013). Generally, an association

between greater levels of early life adversity and differential DNA methylation has been reported (Cecil et al. 2020; Jawahar et al. 2015; Kinnally et al. 2011; Park et al. 2019; Turecki & Meaney 2016). Many studies focus on methylation profiles among specific genetic loci involved in neuronal development (e.g. *BDNF, KITLG*, etc.) HPA axis regulation (e.g. *NR3C1, FKBP5, BDNF, CRHR1*, etc.), neurotransmission (e.g. *AVP, 5HTTR, OXTR, SLC6A4*, etc.).

Evidence in human studies suggest that differential methylation in key HPA axis-related regulatory genes (Table 1) in adulthood is associated with adult hormonal, inflammatory, and neurotransmitter levels in human saliva, blood, and cerebral spinal fluid (Albert & Benkelfat 2013; Heim & Binder 2012; Keller et al. 2017; Smith et al. 2011; Uddin et al. 2015). Sustained changes in circulation of these molecular regulators of human stress physiology, such as corticosteroids, catecholamines, and stress-related peptide hormones like corticotropin-releasing hormone and adrenocorticotropic hormone, are characteristics of stress-induced adult depression and resilience (Feder et al. 2009; Nantharat et al. 2015; Southwick et al. 2005). Research shows that differential methylation of stress response genes may contribute to the lasting effects of early life stress, alter production and regulation of neurotransmission and stress-related neuroendocrine factors, and increase one's disease risk and susceptibility to neuropsychiatric conditions across the lifespan (Heim & Binder 2012; Jawahar et al. 2015; Khulan et al. 2014; Lutz et al. 2015; Provencal & Binder 2015).

Structural pathways

Structural alterations in the brain represent another major neuropathological mechanism of depression. Scientists have largely focused on the cortical and hippocampal regions of the brain. In structural magnetic resonance imaging (MRI) and postmortem studies, these regions

exhibit subtle atrophy in depressed individuals, which is a result of a smaller neurons, lower dendritic density and neurotrophic factor concentration, and fewer glial cells in these regions. An integration of recent neuroanatomical data suggests a collection of major "circuits" in the brain precipitate the emotional symptoms of depression.

Two major heuristics have emerged: a) an amygdala-centric circuit (Savitz & Drevets 2009) and b) a model developed from functional imaging studies (Mayberg 2009). The amygdala-centric circuit – largely informed by structural imaging and postmortem data – suggests that the functional impairment of the striatum, prefrontal cortex, and orbital prefrontal cortex produce the emotional characteristics of depression. Additionally, dysregulation of the prefrontal cortical networks potentially caused by a functional hypersensitivity of the amygdala represents another pathway that shapes the emotional characteristics of the disease.

The second heuristic suggests that four clusters of anatomically-connected brain regions, each representing four major depressive endophenotypes – 1) exteroceptive, 2) interoceptive, 3) mood-monitoring, and 4) mood-regulating, represent the brain circuits that produce the major symptoms of depression. Importantly, Krishnan & Nestler (2010) caution that these simplified heuristics do not fully capture the heterogeneity within the molecular, neurotransmitter, and cellular pathways of brain circuits. The neurobiology of depression using the latest technological and analytical techniques hold massive promise for elucidating the structural roles and pathways of stress and depression.

Table 2. Additional Biologic Theories of the Pathophysiology of Depression.*

Theory	Supporting Evidence	Contradictory Evidence
Altered glutamatergic neurotransmission	Glutamate and glutamine levels in the prefrontal cortex are reduced[91]	Glutamate levels in the occipital cortex are increased[92,93]
	Intravenous ketamine, an NMDA antagonist, induces rapid, sustained antidepressant effect [94]	Ketamine binds to high-affinity-state D2 dopamine receptors[95]
	Cortical messenger RNA levels of glutamate transporters and of the enzyme that converts glutamate to glutamine are reduced[96]	It is not clear whether antidepressants affect AMPA receptors in the brain[97]
Reduced GABAergic neurotransmission	Levels of GABA in plasma, cerebrospinal fluid, the dorsolateral prefrontal cortex, and the occipital cortex are reduced[91-93]	GABA occurs in more than 30% of brain synapses, suggesting nonspecificity
	GABA-modulating agents have effects in animal models of depression[98]	There is a lack of difference in prefrontal cortex GABA levels on MRS in depression[99]
	Antidepressants affect GABAergic function[98]	GABA neurotransmission may be related to symptoms of anxiety in depression
	GABA neuron immunoreactivity is reduced in the prefrontal cortex[100]	
Abnormal circadian rhythms	Sleep deprivation and light therapy have antidepressant effects[101,102]	The association between clock-related genes and depression is inconsistent[103]
	Some patients with depression have circadian abnormalities of mood, sleep, temperature, and neuroendocrine secretion[104]	
	Rodents active during the day become depressed when daylight is shortened[105]	
Deficient neurosteroid synthesis	Cholesterol levels are low in plasma and the brain during depression[106]	The findings in schizophrenia are similar[107]
	DHEA has antidepressant effects in patients with depression[108]	Neurosteroids (neuroactive steroids in the brain that modulate neurotransmitter receptors) mostly affect memory and sleep
Impaired endogenous opioid function	δ-Opioid–receptor agonists have antidepressant-like effects in rodents and up-regulate levels of BDNF in the brain[109]	Although early reports suggested that opiates may be effective in treating depression,[110] data from large, controlled, randomized trials are lacking
	Capacity for cortical μ-opioid–receptor binding is decreased in response to sustained sadness[111]	
Monoamine–acetylcholine imbalance	Depressed mood can be induced in humans by administration of physostigmine, an acetylcholinesterase inhibitor[112]	Mecamylamine, a nicotinic acetylcholine receptor antagonist, reduced symptoms of depression[113]
	Nicotinic acetylcholine receptor antagonists potentiate antidepressants[114]	Many antidepressants are not anticholinergic
Cytokine-mediated cross-talk between the immune system and the brain	Depression is common in infectious and autoimmune diseases[115]	Most studies are correlative[116]
	Exposure to cytokines induces depressive symptoms, and cytokine secretion is increased in major depression[115]	Cytokine-induced depressive symptoms are temporary and not replicated in all studies[117]
	Antidepressants have antiinflammatory effects[115]	Substance P antagonists are not therapeutic in depression
	Cytokines affect the hypothalamic–pituitary–adrenal axis and monoamines[115]	
Thyroxine abnormalities	Levels of transthyretin are reduced in the cerebrospinal fluid in patients with depression[118]	
	Thyroid hormones modulate the serotonergic system in the brain[119]	Thyroxine monotherapy is ineffective
	Brain neurogenesis is decreased after the administration of thyroxine in adult rats with hypothyroidism[120]	Hypothyroidism is not manifested in most patients with depression
	Rate of response to triiodothyronine is increased during depression[121]	
Dysfunction of specific brain structures and circuits	Transcranial magnetic stimulation of the prefrontal cortex[122] and deep-brain stimulation of the anterior cingulate affect mood[123]	Implicated brain areas differ from study to study
	Glucose use is reduced in the prefrontal cortex[124] and subgenual prefrontal cortex[125]	Inconsistent findings with respect to blood flow, volumetric, glucose utilization, and postmortem methodologies[63,124,126]
	Circuit dynamics in the hippocampus are altered in a rat model of depression[127]	

* AMPA denotes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BDNF brain-derived neurotrophic factor, DHEA dehydroepiandrosterone, GABA γ-aminobutyric acid, MRS magnetic resonance spectroscopy, and NMDA *N*-methyl-D-aspartic acid.

Figure 2. Additional biologic theories of the pathophysiology of depression (Belmaker & Agam 2008)

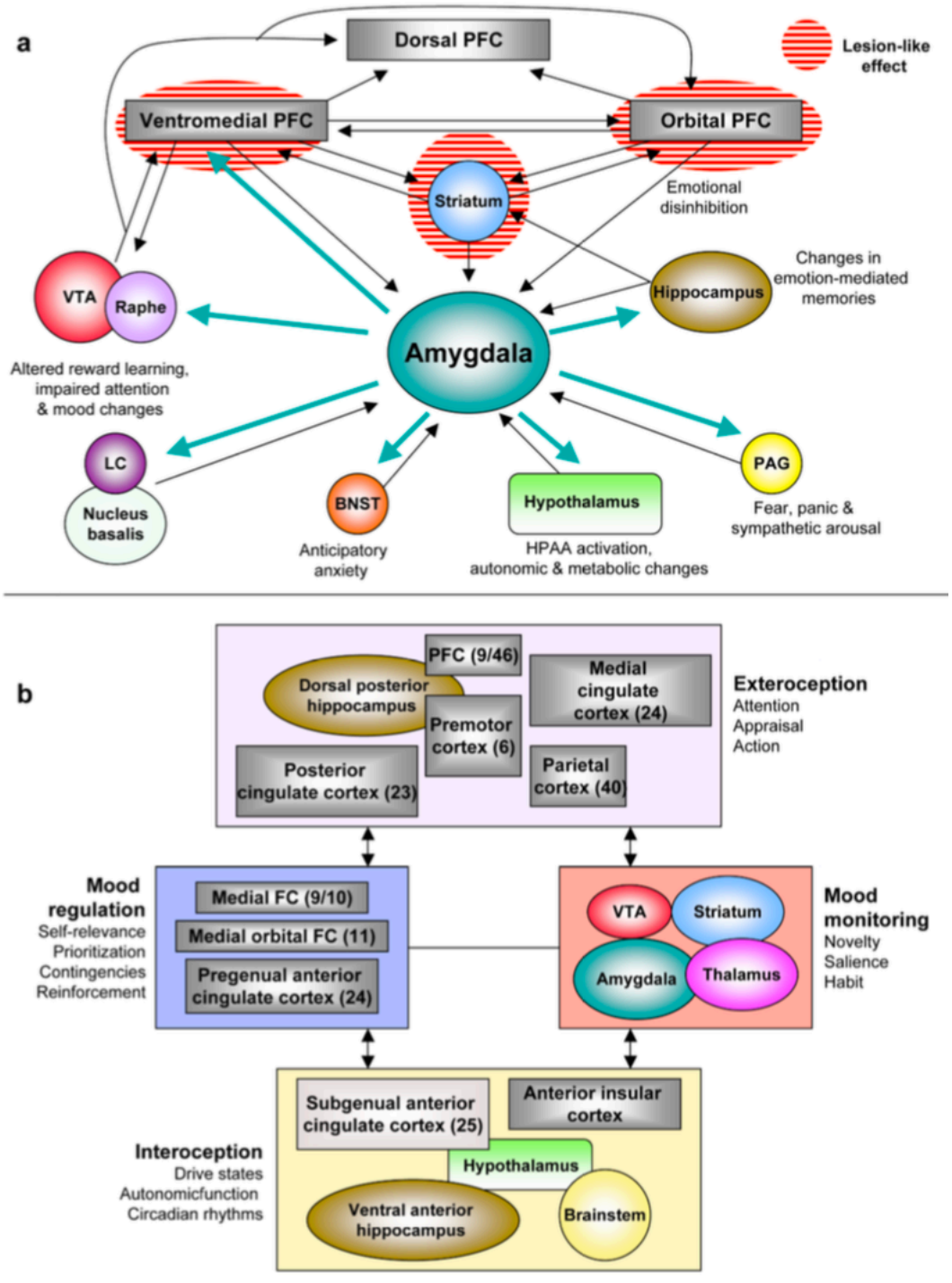


Figure 3. Two major circuit-based heuristics of depression (Model A: Savitz & Drevets 2009; Model B: Mayberg 2009).

2.4 Developmental origins of adult HPA axis function and depression: Early life and intergenerational effects

Recent theoretical advancements in developmental biology, public health, psychology, and medicine have introduced new hypotheses to understand the mechanisms that drive the emergence of physical and mental illnesses across the lifecourse. This framework has become known as the "developmental origins of health and disease (DOHaD)," which argues that the quality of early life conditions, particularly those that occur during fetal development, are strong predictors of future developmental biology, health, and disease risk across one's lifecourse (Barker 1990; Kuzawa 2005; Worthman & Kuzara 2005). The DOHaD framework first emerged after seminal findings in epidemiology identified that intrauterine conditions, such as fetal undernutrition and stress, were important predictors of adult cardiovascular and metabolic disease in the next generation (Barker et al. 1989; Barker et al. 1993). Since Barker's seminal findings, DOHaD has become a burgeoning field of study in various disciplines, including biological anthropology, biology, public health, and medicine, and DOHaD research has highlighted the major role of early stress, intrauterine conditions, and external environments in durably shaping a wide range of biological and phenotypic outcomes across the child's lifecourse (Kuzawa et al. 2007; Kuzawa & Quinn 2009; McDade 2012; O'Donnell & Meaney 2017; Said Mohamed et al. 2018). The developing organism depends on environmental inputs to calibrate one's biology and behavior, which has corresponded with the development of sophisticated stress-sensitive ontogenetic structures throughout evolution (West-Eberhard 2003).

The long-term developmental effects of early stress exposure represent a larger process of human adaptability that biological anthropologists and other developmental researchers know as "phenotypic plasticity." Biologist Mary Jane West-Eberhard defines as phenotypic plasticity

as “the ability of an organism to react to an internal or external environmental input with a change in form, state, movement or rate of activity” (West-Eberhard 2003:33). Developmental plasticity, a form of phenotypic plasticity, is a process that allows organisms to adjust their physiology and developmental trajectories based on timescales of adaptation that are too slow and too chronic for homeostasis and genetic natural selection to address, respectively (Kuzawa & Pike 2005). As Kuzawa and Pike (2005:225) state, “these mechanisms [of developmental plasticity] can be viewed as allowing the organism to fine-tune structure, function and regulatory set points to match the needs imposed by an individual’s idiosyncratic behavioral patterns, nutrition, stress and other environmental experiences, none of which can be anticipated in detail by the genome inherited at conception.” For instance, while genetic change via natural selection allows organisms to respond to longer-term environmental signals, such as environmental stress, maternal trauma, and molecular signals, phenotypic plasticity allows for more rapid adjustments to environmental changes that occur over shorter timescales (Kuzawa & Thayer 2011). DOHaD has both emerged out of and developed alongside and this broader theoretical framework of organismal development and lifecourse health and provides a strong theoretical framework to elucidate how and why maternal experience influences intergenerational outcomes in biology and health.

The role of fetal development as period of intergenerational signaling and major predictor of future health and biology is a recent and burgeoning area of research focus in biological anthropology, developmental biology, and medicine (Blake 2018; Kuzawa 2020; Kuzawa & Thayer 2011; McKerracher et al. 2020; Mulligan 2016; Norris et al. 2012). Because gestation is a developmental period when the fetal environment is the mother’s body (Mastorakos & Illias 2003), such as maternal nutrition or stress, the transmission of environmental influences

operating through maternally-mediated biological but non-genetic pathways – a proposed mechanism of stress-initiated developmental plasticity – is possible (Love & Williams 2008; Beydoun & Saftlas 2008; Kuzawa & Quinn 2009). A growing yet powerful body of scholarship from DOHaD and other scholars suggests that psychosocial stress and social adversity experienced early in life, and possibly during gestational development, may increase one's risk of mental illness during their adulthood and among reproductively aged women, may influence the gestational environment experienced by the next generation, thereby influencing grandoffspring development. Thus, maternal exposures during gestation may not only affect their developing children but also affect the health and biology of subsequent generations - thus describing a possible intergenerational mechanism for stress transmission (Kuzawa & Sweet 2009; Kuzawa 2020).

The hypothalamic-pituitary-adrenal (HPA) axis

Understanding the basic structure and function of the primary physiological system of stress regulation is necessary to understand its role in shaping offspring stress functions and physiological outcomes. The HPA axis is a collection of structures that produce and facilitate a complex set of dynamics across three endocrine glands: the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland. The HPA axis serves as the major neuroendocrine system that controls the stress ("fight-or-flight") response and regulates a variety of downstream physiological processes which represent adaptive responses to stress, including the immune system, energetics, osmoregulation, and behavior, among other adaptive processes. These processes occur as a result of the alteration of the HPA axis via expression of hypothalamic corticotropin-releasing factor (CRF), which stimulates the

secretion of adrenocorticotropic hormone (ACTH) in the pituitary glands. ACTH travels through the bloodstream and stimulates the zona fasciculata in the adrenal glands, which in turn produces glucocorticoids, cortisol being the most well-known and well-studied glucocorticoid. The HPA axis is present in vertebrate animals, derives from a deeply conserved system of homeostasis, and mediates the effects of environmental exposure in organisms both in the same and next generation, as discussed below (Denver 1999; Denver 2009).

Cortisol circulation during times of stress initiates a suite of adaptive responses, such as increased blood pressure, dilated pupils, and the mobilization of fat storages for energy. The changes in basal cortisol levels and HPA axis activity among offspring has been interpreted as a possible adaptation to environmental stressors experienced by the mother during gestation and potentially due to stressors experienced throughout her lifecourse (Berghänel et al. 2016; Glover 2011; Sheriff & Love 2013; Thayer et al. 2018). Studies across various vertebrate species have shown that the mother's past and current experiences may intergenerationally shape the phenotype of her offspring through HPA axis pathways without genetic changes. For example, in the case of the European starling, maternal quality was indirectly related to maternal baseline GC and yolk GC levels, which led to smaller size at birth, slower growth, and increased early postnatal mortality. Though the resultant offspring phenotypes consisted of negative health and physiological outcomes, male starlings paired with low-quality mothers exhibited greater fitness characteristics compared to control pairs (Chin et al. 2009; Love et al. 2008).

Additionally, in an impressive 10-year naturalistic study of snowshoe hares, prenatally-stressed mothers gave birth to fewer and smaller progeny with higher stress reactivity during a period directly preceding low predator risk (Sheriff et al. 2009). This stands in contrast to prenatally-stressed mothers who gave birth to similar offspring during a period of high predator

density (Sheriff et al. 2011). These examples highlight the role of the HPA axis in physiologically responding to environmental conditions and also the adaptive potential of the system for organisms and their offspring, though more theoretical and empirical work is needed to determine the evolutionary significance of these intergenerational effects and the extent to which these outcomes are adaptive and/or pathological.

As the HPA axis-mediated stress response was designed to respond to short, intermittent stressors, chronic activation of the HPA axis through repeated stress exposure can lead to maladaptation of the stress response, also known as HPA axis dysregulation, leading to toxic effects on tissues throughout the body that contribute to the onset of disease (Sapolsky 2000; Charmandari et al. 2005).

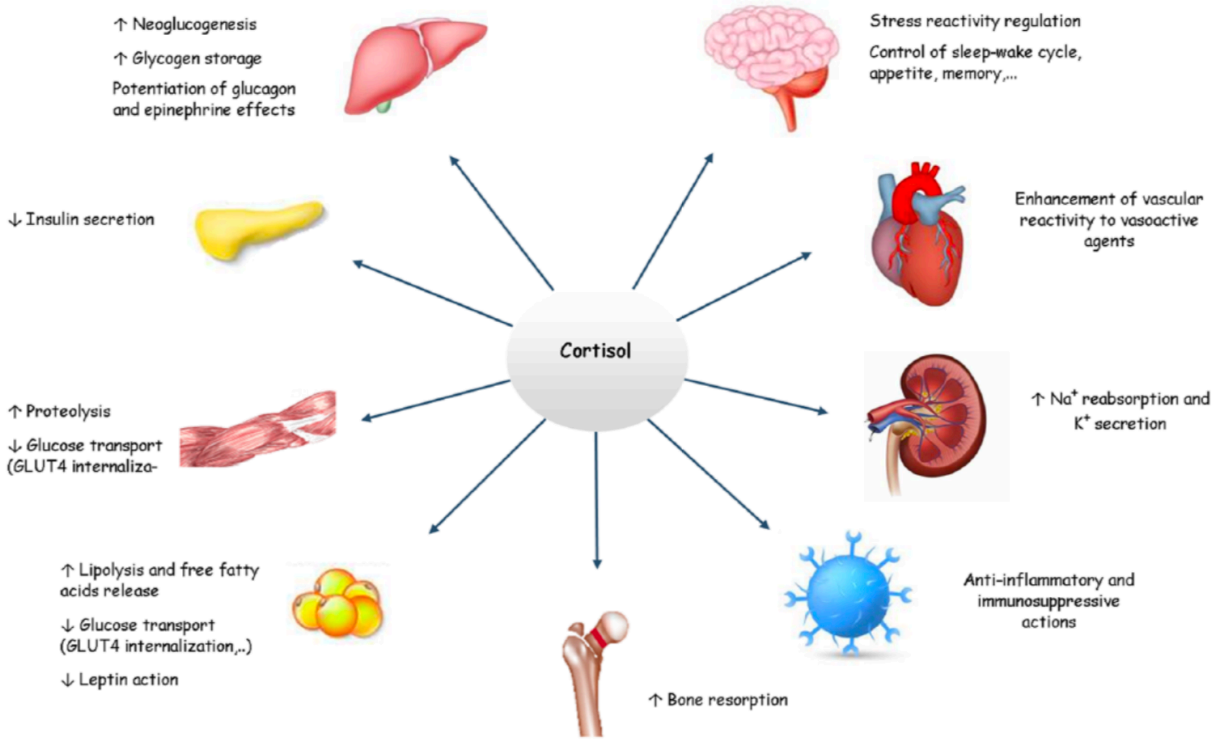


Figure 4. Physiological impacts of cortisol in the human body (Oprea et al. 2019).

Animal studies: Early stress, HPA axis function, and behavior

The study of the fetal origins of adult neuroendocrine activity and mental health has become a major focus of developmental, biological, and medical research over the past three decades. Decades of animal-based research in non-mammalian and mammalian vertebrate studies, especially research on murine species and non-human primates, strongly suggest that maternal prenatal stress and postnatal early life adversity are potent risk factors for altered postnatal neuroendocrine activity and later life psychiatric outcomes (Circulli et al. 2009; Glover et al. 2010; Maccari et al. 2003; Monk et al. 2019). Between the 1970s and early 2000s, researchers studying the HPA axis in mice models gathered strong evidence on the prenatal stress-linked elevations of basal corticosteroids - a steroid hormone that is homologous to the stress and metabolic hormone in humans known as cortisol - corticosteroid reactivity to laboratory stressors, and decreased sensitivity of the negative feedback process in the HPA axis (Francis et al. 1999; Fride et al. 1986; Joffe 1978; Maccari et al. 1995; Meaney 2001; Welberg & Seckl 2001). Furthermore, greater prenatal stress has been found to alter stress neurocircuitry in mice, altering corticotropin-releasing factor (CRF), a major peptide hormone of the HPA axis, in the amygdala and glucocorticoid receptor expression in the hippocampus (Weinstock 2008), which are major correlates and precursors to adverse cognitive outcomes in offspring across the lifecourse, including depression- and anxiety-like behaviors (Weinstock 2008).

While rodent-based research has largely informed our current understanding of the biobehavioral effects of early life stress, rodent models present major limitations in comparison primate and human biology (Parker & Maestripieri 2011). The HPA axis development of rodents as well as the neurobiological substrates of cognitive-based behavior and emotion regulation are drastically different compared to both nonhuman and human primates (Preuss 1995; Ongur &

Price 2000). Conversely, experimental and naturalistic studies of non-human primates have made major contributions to current understandings of resilience among humans, particularly in the form of behavioral, developmental, and increasingly, biological perspectives. The close evolutionary relatedness, shorter lifespan, and complex sociality of primates make them an excellent animal model to study the social and biological contributions to behavior and health (Parker & Maestripieri 2011). Additionally, the extended postnatal maturation period of primates provides ample time for developing neurobiological systems to be shaped by one's experience (Nelson & Bloom 1997).

Compared to rodent studies, the literature on captive and wild non-human primate have similarly documented long-term offspring neuroendocrine and psychological impacts due to prenatal and postnatal stress across a variety of species (Meyer & Hamel 2014; Parker & Maestripieri 2011). Substantial evidence shows that greater prenatal stress in non-human primate samples correspond with altered offspring HPA axis reactivity (Clarke et al. 1994; Coe et al. 2003; Murray et al. 2016; Uno et al. 1994) and social behavior across the offspring's lifecourse (Bardi & Huffman 2005; Bauman et al. 2014; Hauser et al. 2008; Hijab et al. 2017), though results on offspring behavior are mixed (Schülke et al. 2019). The effects of postnatal early life stress are similar to the literature on prenatal stress in non-human primates. For instance, one prominent study of captive mother-infant rhesus macaques found that repetitive maternal separation between the ages of three to six months resulted in in mother-infant interactions, increased anxiety-like behavior, increased cortisol reactivity in female infants, and flattened diurnal cortisol slopes at 12 months (Sánchez et al. 2005). Finally, a recent prospective study in wild female baboons reported that early adversity strongly predicted raised fecal glucocorticoid levels in adulthood (Rosenbaum et al. 2020).

The general positive association between early stress and later-life cortisol function and mood may represent a broader phylogenetic trend across vertebrate species. A recent meta-analysis that assessed findings from 14 vertebrate species found small-to-moderate effects of maternal prenatal stress on offspring levels of glucocorticoids – a class of corticosteroids – after an environmental or laboratory stress exposure (Thayer et al. 2018; Figure 1). Given the consistent trend in the intergenerational effects of stress seen across species, as the authors speculate that this development response may have deeper evolutionary implications:

> "These findings are therefore consistent with an ancient vertebrate origin of HPA-axis programming, and suggest that such effects may have been selected for to mediate intra-specific variability in life history strategy. Given the similarities in programming capacity across vertebrates, this suggests that both mammalian and non-mammalian model organisms may be appropriate for developing a detailed understanding of prenatal programming of HPA-axis function in humans." (Thayer et al. 2018:5).

While findings from vertebrate studies highlight the vast variation in the durable effects of prenatal stress due to several qualities of the exposure (e.g. timing, duration, severity, type, social rearing environment, and the ecological validity of the stressor) (Glover et al. 2010; Parker & Maestripieri 2011), the overall trend in studies of vertebrate studies generally shows that greater maternal prenatal stress is associated with altered HPA axis function and adverse behavioral patterns across the offspring's lifecourse. Decades of animal research have greatly informed and advanced our understanding of the long-term intergenerational impacts of maternal prenatal stress in humans. In the following section, I describe the phylogenetic development of

the HPA axis in vertebrates and explain the functional roles and pathways of the major neuroendocrine hormones that orchestrate the system.

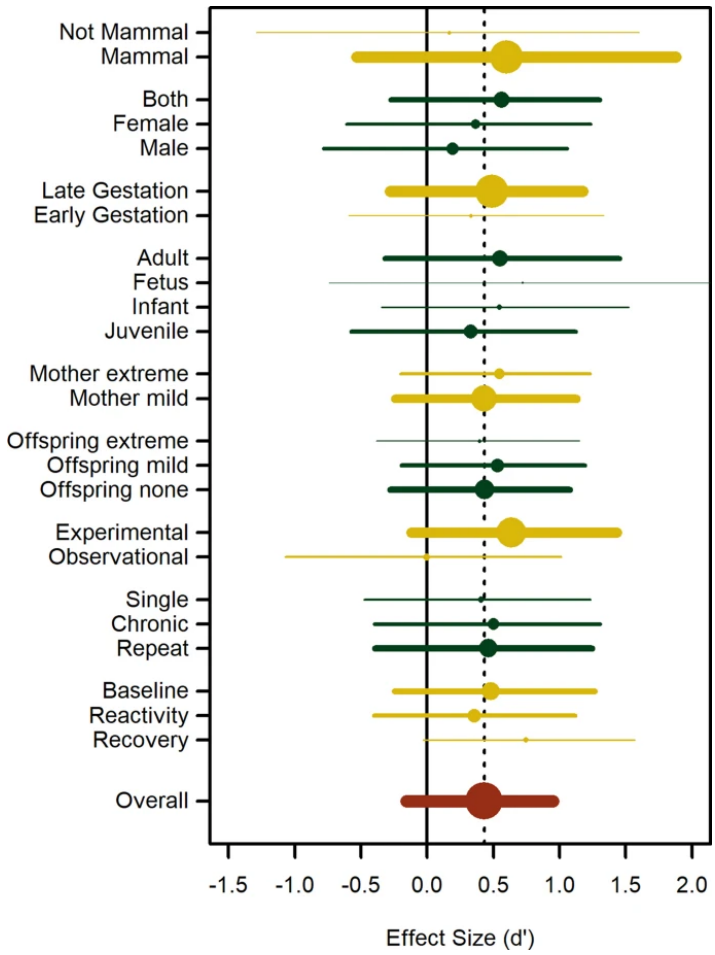


Figure 5. This figure highlights the evolutionarily conserved nature of heightened infant cortisol reactivity as a result of increased maternal prenatal stress. The following graph shows results from a meta-analysis on the impacts of prenatal stress on offspring cortisol reactivity across 14 mammalian species, which highlights a positive effect size, suggesting the deeply conserved adaptive qualities of this system (Thayer et al. 2018).

2.5 Intergenerational mechanisms of prenatal stress, adult HPA axis function, and mental health

Phylogenetic evolution of the vertebrate HPA axis: structure and function

The key structure and functions of the human HPA axis were likely already active among the earliest vertebrate species and have since been maintained by natural selection (Denver 2009). These include the presence of an HPA axis-like physiology, chemical products including corticosteroids (e.g. glucocorticoids and mineralocorticoids) and their corresponding receptors, and characteristic functions such as the stress response and recovery. The ancient origins of the HPA axis anatomy are reflected by the many genes of the HPA axis present in extant urochordates and cephalochordates and are seen to predate chordates (Stefano et al. 2002; Lovejoy & Jahan 2006). Additionally, the presence of tissues capable of corticosteroidogenesis is found in vertebrates as early as chondrichthyes (Wendelaar 1993). In a majority of more recent vertebrate species, corticosteroidogenic tissues form distinct organs called interrenal glands, which are the mammalian equivalent to the adrenal glands, begin to appear (Norris 2006). Overall, the production of CRF-like neuropeptides in the hypothalamus and its downstream effects of ACTH and corticosteroid release are seen across all vertebrate models in the literature.

Stress-induced expression of CRF genes is likely to have developed in the early stages of vertebrate evolution. Stress exposure increased CRF mRNA concentrations in the pre-optic area (POA) of the hypothalamus and elevated CRF levels in systemic circulation of teleosts (Yao & Denver 2007; Dautzenberg & Hauger 2002). Similarly, immediate increases in CRF heteronuclear RNA (hnRNA; a form of pre-mRNA), CRF mRNA, and CRF peptides were reported in the POA/hypothalamic neurosecretory neurons of rodents and frogs (Yao & Denver 2007). Several molecular mechanisms involved in stressor-dependent activation of CRF-like

peptide genes are also seen to be conserved across vertebrates. These include high sequence similarity of the promoter regions of CRF genes and transcription binding sites, cAMP activation of the CRF genes, expression of the transcription factor Fos via the protein kinase C pathway, and the upregulation of nerve growth factor induced gene B (*NGFI-B*), which has been implicated in the regulation of CRF gene expression (Yao & Denver 2007).

Stress regulation has also been conserved and plays an important adaptive role in homeostatic control, particularly in mammals (Denver 2009). GCs negatively regulate the hypothalamic PVN and the anterior pituitary by directly acting on the CRF neurons to reduce CRF synthesis and release and on corticotropes to decrease synthesis of pro-opiomelanocortin (POMC) and downstream release of ACTH (Fulford & Harbuz 2005). While the process of negative feedback is well-documented in mammals, research on GC feedback processes in non-mammalian species are sparse (Denver 2009). The limited data on non-mammalian species, however, align with findings on mammalian stress biology that strongly support GC regulation of hypophysiotropic CRF neurons (Denver 2009). For example, in frogs (*Xenopus laevis*), *in vitro* and *in vivo* studies confirmed that proximal CRF promoters are negatively regulated by GCs and that the composite genetic sites for the glucocorticoid response element for the activator protein-1 transcription factor are both structurally and functionally conserved in the frog genes (Stenzel-Poore et al. 1992). Additionally, several studies of teleost fishes have shown negative regulation of CRF by GCs, though the molecular mechanisms are unknown (Bernier et al. 2004; Denver 2009). Collectively, these studies suggest that characteristic functions of stress regulation have been evolutionarily maintained (Thayer et al. 2018), though more studies in non-mammalian vertebrates are necessary to confirm the likelihood of phylogenetic conservation (Denver 2009).

A clear lineage of HPA axis development and persistence across vertebrate evolution emphasizes its critical role in animal survival and maintenance. When looking at the patterns of intergenerational stress transmission, the strong phylogenetic conservation of HPA axis function is seen to extend beyond a single generation of an organism into the stress physiology of the developing fetus and future offspring. That is, the dynamics of the HPA axis, namely the effects of CRF and GCs, shape the phenotype of offspring during development and are seen to have similar adaptive qualities that have been conserved across vertebrate evolution (Denver 2009).

Developmental effects of CRF and corticosteroids

Both CRF and GCs play essential roles in mediating an organism's interaction with and embodiment of the environment during ontogenesis. CRF and CRF-like peptides, such as urocortin (a protein whose corresponding gene is a homologue to the human *CRF* gene), orchestrate behavioral, morphological, and physiological homeostatic responses to the shifting conditions of the environment. Corticosteroids exhibit similar environmental regulatory functions to CRF. As mentioned earlier, corticosteroid levels increase as part of the stress response across taxa. Corticosteroids mobilize energetic resources and elevate metabolic rate as an adaptive, urgent response to drastic stress exposure (Wingfield et al. 1998). Glucocorticoids, a particular class of corticosteroids, are commonly identified as "stress" hormones, though a primary metabolic function of baseline GCs is to regulate circulating glucose levels (Sapolsky et al. 2000). Additionally, elevated GCs levels mobilize energy stores during life stage transitions and facilitate responses to environmental shifts (Sheriff & Love 2012). These multifaceted and adaptive roles emphasize the functions of CRF and corticosteroids as key players of larger

homeostatic mechanisms and evolution (Crespi & Denver 2005). Their role as ancient, developmentally significant signaling molecules for offspring ontogenesis is distinct.

Corticotropin-releasing factor

The interesting work on the environmental regulation of larval amphibian development provides a clear example of the adaptive role of CRF in mediating the relationship between environmental stress exposure and offspring early life development. Denver (1988) was the first to implicate CRF in altering metamorphosis via neuroendocrine regulation of the HPA/I (interrenal) axis and the HPT (hypothalamic-pituitary-thyroid) axis when he found that CRF stimulates thyroid stimulating hormone (TSH) in frog pituitaries. CRF-induced TSH release is seen across most species of non-mammalian vertebrates (De Groef et al. 2006). CRF was also found to play a role in accelerating metamorphosis by acting on T_3 thyroid hormone, a well-known factor in controlling metamorphosis, and corticosteroid production (Boorse & Denver 2003). Similar accelerating effects of CRF were seen in tiger salamanders. Ovine CRF-treated larvae achieved metamorphosis faster than saline-injected larvae (Boorse & Denver 2002).

CRF is also known to consistently vary across numerous life stage transitions across species. For example, CRF has been reported to increase during smoltification, the transition from living in freshwater to saltwater, in the POA of Atlantic salmon compared to non-smolting salmon. In chickens, hypothalamic levels of CRF mRNA declined before hatching then increased after hatching (Lu et al. 2008; Vandenborne et al. 2005). Finally, *CRF* gene expression in rodents is seen to increase towards parturition and decrease afterwards (Baram & Lerner 1991), yet the role of CRF on stimulating parturition is unclear (Funai et al. 2000). Similar to amphibian

development, CRF plays a key role in shaping maturational tempo and key life stage transitions across taxa but its intricate organizational effects are beyond the scope of this paper.

Corticosteroids

Corticosteroids play similar developmental roles as CRF in vertebrate species. Glucocorticoids, a class of corticosteroids, seem to be more involved in hatching and parturition. Corticosterone peaks before hatching in birds (Scott et al. 1981; Frigerio et al. 2001) and reptiles (Jennings et al. 2000; Medler & Lance 1998), and some researchers suggest that corticosterone may be required for hatching in oviparous species. Corticosterone injections in turkey embryos increase hatching success and decrease incubation periods. Tree lizard-treated eggs hatch significantly faster. "Large" egg fish species like salmon also increase ACTH and cortisol around hatching. Conversely, "small" egg fish such as sea bass and the gilthead sea bream exhibit low or declining corticosterone levels until hatching (Perez et al. 1999; Szisch et al. 2005). Wada (2008) interprets this trend in fish as a potential effect of life history strategies, with larger and fewer offspring-generating fish already having a mature HPI axis, which results in a GC-involved initiation of hatching. Fetal GCs release also initiates a complex cascade that leads to parturition. ACTH and fetal GCs spike prior to birth across numerous animals species, including rodents (Martin et al. 1977; van Baelen et al. 1977), sheep (Bassett & Thorburn 1969; MacIsaac et al. 1985), pigs (Heo et al. 2003), and humans (Yoon et al. 1998; Murphy & Clifton 2003).

Kikuyama et al. (1993) found that corticosteroids also interact with amphibian larval thyroid hormone (T_3) to accelerate metamorphosis, which implicated corticosteroids in faster maturation. This idea was further supported by studies that reported that stressful environmental conditions known to elevate corticosteroid levels, such habitat desiccation, crowding, and

resource restriction, also accelerated metamorphosis (Denver et al. 2002). Flatfish larvae also exhibited faster maturation when treated with ACTH or corticosterone injections in conjunctions with thyroid hormones (Brown & Kim 1995). Importantly, the developmental effects of these neuroendocrine hormones were temporally dependent for tadpoles. Adverse environmental conditions experienced during premetamorphosis slowed tadpole development, which was mediated by elevated corticosteroids (Glennmeier & Denver 2002). In contrast, environmental stress (i.e. water volume reduction and food restriction) is associated with accelerated metamorphosis closer towards the metamorphic climax, also mediated by elevated corticosterone and CRF levels (Denver 1997a; Denver 1998). These neuroendocrine-mediated shifts in maturational tempo play an adaptive role in maximizing survival for this species of Western spadefoot toad tadpoles, which are found in desert ecosystems. Overall, these data on hatching, parturition, life stage transitions, and maturational tempo emphasize the central role of the HPA axis in facilitating the environmental regulation of organismal development as well as its potential evolutionary significance.

In the following sections, I describe the stress physiological mechanisms that are understood to facilitate the long-term impacts of prenatal stress across the lifecourse, with a particular focus on the HPA axis. I begin with a description of pregnancy and various stress-sensitive *in utero* mechanisms including fetal growth and preterm birth. I then review the literature on the effects of prenatal stress during infancy and childhood, then move to describe the nascent yet growing literature on adult programming effects. Finally, I illustrate the possible neuroendocrine mechanisms that may underlie the long-term effects of prenatal stress on the adult offspring's own pregnancy, thus tracing a possible intergenerational mechanism of prenatal stress across three generations - the primary theoretical contribution of this dissertation.

2.6 Prenatal stress, fetal development, and birth outcomes: biological mechanisms

Pregnancy and parturition

A gestating mother reaches full term at approximately 38.5 weeks. Over the course of the pregnancy, levels of progesterone gradually increase to relax the smooth muscle of the uterus in order to prevent premature contractions and delivery (Challis et al 2001). After about 37 weeks, progesterone concentrations decrease while estrogen levels, which gradually elevates over the course of the pregnancy, continues to increase. The estrogen and progesterone ratio sensitize the uterus to other hormones like oxytocin, which contributes to the onset of uterine contractions. As the fetus develops and gains weight, the fetus descends lower into the uterus, eventually making contact with the cervix and subsequently stimulating uterine contractions and cervical dilation and effacement. During this time, the placenta also secretes a hormone called relaxin, which contributes to the loosening of the pelvic ligaments to provide space for the enlarging uterus, the opening of the pelvic outlet by loosening the public symphysis joint between both parts of the pelvis, and the dilation of the cervix during labor.

There are three main stages of parturition (or labor): cervical dilation, expulsion of baby, and afterbirth. The duration of parturition ranges from seven to twenty hours, and longer for some mothers. Uterine contractions stimulated by elevated circulating levels of oxytocin released from the posterior pituitary gland cause membranes surrounding the fetus to release additional hormones called prostaglandins that serve to soften the cervix and further stimulate uterine contractions. Thus, oxytocin-stimulated contractions lead to greater production of prostaglandins, which in turn leads to stronger and more frequent contractions, thus generating a positive feedback loop of endocrine production and contractions. (Challis et al 2001; Hillhouse & Grammatopoulos 2002; Smith et al. 2002). The upward direction of uterine contractions pull the

cervix thinner, open the cervix, and also pushes the fetus against the cervix, contributing to greater dilation. Increased relaxin production also dilates the cervix. The mucous layer that seals the cervix is expelled and the amniotic sac is ruptured, causing amniotic fluid to exit the vagina. As the contractions become stronger and closer together and once the cervix dilates to ten centimeters, the mother develops an urge to push the baby out, leading to the second phase of parturition, the expulsion phase. The expulsion phase begins when the fetal head enters the birth canal and ends with the expulsion of the neonate. Once the baby is born, the last stage of parturition, the afterlife, begins. Uterine contractions continue until the placenta is expelled and involution, or the shrinking of the uterus to pre-gestation size, initiates.

Fetal development, preterm birth, and intrauterine growth restriction: the role of the HPA axis

Psychosocial stress exposure during earlier windows of gestation may lead to decreases in birthweight due to HPA axis-mediated fetal growth restriction and earlier parturition (D'Anna-Hernandez et al. 2012; Glynn et al. 2001). The mechanisms underlying the impacts of maternal HPA axis function on fetal development, however, are only partially understood (Gitau et al. 2001). Three potential mechanisms have been suggested: maternal cortisol exposure through the placenta, downregulation of cortisol-shielding enzymatic mechanisms, and reduced stress reactivity across pregnancy. First, stress-initiated elevations in circulating glucocorticoids (GCs) may lead to greater levels of cortisol to move through the placenta and reach the fetus (O'Donnell et al. 2009). Greater maternal cortisol levels during early periods of pregnancy have been associated with being SGA (Goedhart et al. 2010) and LBW (Bolten et al. 2011; D'Anna-Hernandez et al. 2012; Goedhart et al. 2010). Contrary to the negative feedback loop between adrenal cortisol exposure and hypothalamic corticotropin-releasing hormone (CRH) production,

higher cortisol exposure increases CRH production in the placenta, which subsequently can upregulate the production of pituitary adrenocorticotropic hormone (ACTH) and in turn, cortisol in both the mother and the fetus (Majzoub & Karalis 1999). Growing evidence also suggests that greater prenatal stress exposure may result in maternal immune dysregulation during pregnancy, which has been associated with adverse gestational development and birth outcomes, including restricted fetal growth, preterm birth, and LBW (Beijers et al. 2014; Nazzari et al. 2019).

Second, early increases in maternal cortisol during gestation may also downregulate fetal buffering mechanisms against maternal cortisol. Placental levels of 11β-hydroxysteroid dehydrogenase (11β-HSD-2) act as a natural shield against maternal cortisol in utero by converting cortisol into biologically inactive cortisone. Maternal cortisol, however, is still able to penetrate the fetus in small amounts particularly when circulating maternal cortisol reaches high concentrations or when 11β-HSD-2 is downregulated (O'Donnell et al. 2012). For instance, recent evidence reports that high levels of maternal GCs can consequently downregulate 11β-HSD-2 production, thus allowing greater passage of GCs, including cortisol, into the womb (O'Donnell et al. 2012). Placental 11β-HSD-2 levels are naturally and relatively low during early gestation (Hobel et al. 2008), and during this time cortisol may more easily pass through the placenta during earlier stages of pregnancy to slow fetal growth rate and shorten GA.

Finally, the impacts of early prenatal stressors on fetal development and birthweight may be heightened as behavioral and biological stress sensitivity decreases among mothers over the course of pregnancy. The sensitivity of both major stress-regulatory systems, the HPA and the sympathetic-adrenal-medullary (SAM) axes, declines as pregnancy advances. For example, mothers in advanced stages of pregnancy show decreased psychological sensitivity (Glynn et al. 2001), HPA axis reactivity (Kammerer et al. 2002; Obel et al. 2005), vascular reactivity to

norepinephrine and epinephrine infusion, lower heart rate and catecholamine responses to physical stressors, and decreased blood pressure responses to stress (Nisell et al. 1985) relative to those in earlier stages.

While increases in maternal cortisol downregulate hypothalamic CRH production, elevations in maternal cortisol may also operate through interactions with the placenta to alter fetal size and birth outcomes. Greater maternal cortisol upregulates placental CRH production during pregnancy (Robinson et al. 1988). Recent studies find that greater levels of placental CRH predict low birthweights (Sandman et al. 2006; Wadhwa et al. 2004). Wadhwa et al. (2004) reported that elevated placental CRH levels at 33 weeks of gestation prospectively predict relative risk for preterm birth and fetal growth restriction after adjusting for the effects of other established risk obstetric factors. For women with elevated CRH at 33 weeks compared to those with normal levels, women faced about a 3-fold increase in the relative risk for delivering a growth-restricted infant. At 33 weeks' gestation, CRH levels at were elevated in three distinct, non-overlapping sets of deliveries: women who delivered preterm but did not have a growth-restricted infant, women who gave birth to a growth-restricted infant but delivered at term, and women who delivered both preterm and had a growth-restricted infant. CRH levels were highest among women in the last group, those who delivered both preterm and growth-restricted infants.

Their findings also suggest that the timing of the onset of parturition may be influenced by events and conditions faced earlier in gestation rather than near the time of parturition: elevated CRH levels predicted preterm birth while lower CRH levels predicted post-term birth. The direct association between placental CRH and the onset of parturition led Wadhwa et al. to conclude that the "placental clock" may be partly facilitated by placental CRH: "Thus, phase advancement of the clock, reflected by elevated placental CRH earlier in pregnancy, may

accelerate the sequence of biomolecular events underlying parturition and result in earlier delivery, whereas phase delay, reflected by lower CRH levels, may lengthen the time to initiate parturition" (Wadhwa et al. 2004: 1067-8; McLean et al. 1995). Placental CRH may regulate fetal growth through its influence on placental perfusion and fetal cortisol production. Increased placental CRH concentrations are also associated with decreased uteroplacental flow and hypoxemia-known risk factors for fetal growth restriction (Giles et al. 1996). Past studies have reported associations between maternal HPA axis products (ACTH, beta-endorphins, and cortisol) and placental CRH levels. Social experiences may also modulate placental CRH levels: maternal psychosocial stress is commonly linked with levels of maternal ACTH and cortisol, and specifically in the third trimester (Wadhwa et al. 1996) and one study has also reported a direct positive association between maternal stress and elevated CRH levels. Thus, as Wadhwa and colleagues argue, "...depending on the chronicity of the stressor, the resulting increase in CRH production may be a critical factor that contributes to the early initiation of parturition and/or growth restriction."

2.7 Prenatal stress, HPA axis function, and adult mental illness risk

Prenatal stress and postnatal HPA axis function

Since DOHaD was introduced, scientists have become interested in the specific mechanisms by which maternal stress and trauma during pregnancy affect the developing fetus and raise future risk for psychopathology. The mechanisms by which prenatal stress impacts future biology and health postnatally is largely understood to operate through maternal-placental-fetal neuroendocrine systems (Cruceanu et al. 2017; Wadhwa 2005). Heightened stress exposure and in some cases, poor regulation of the HPA axis can alter circulating maternal cortisol levels,

which can pass through the placenta at low levels and penetrate the fetus to reach the developing fetal HPA axis (Cruceanu et al. 2017; Krontira et al. 2020; Stroud et al. 2016). Maternal cortisol may be more likely to reach the fetus when stress is experienced earlier in gestation as concentrations of cortisol-inactivating placental 11β-hydroxysteroid dehydrogenase (11β-HSD) are low and maternal sensitivity to stress, which declines over the course of pregnancy, is still normal. Increased fetal cortisol exposure is understood to influence intrauterine growth restriction and contribute to decreased gestational durations, which in turn result in poor birth outcomes (e.g. low birth weight and length, smaller head circumference, higher risk of infant morbidity and mortality, etc.) (Bussières et al. 2015; Ding et al. 2014; Shah et al. 2010).

As previously mentioned, a scarce, but growing, literature is beginning to document the long-term impacts of fetal cortisol exposure across the lifecourse, ranging from fetal development to late adulthood. Past studies have shown that elevated intrauterine cortisol exposure corresponds with alterations in later life HPA axis function in infancy (O'Connor et al. 2013; Thayer & Kuzawa 2009), childhood (Gutteling et al. 2004, 2005; Ping et al. 2015), adolescence (O'Conner et al. 2005; Ping et al. 2020), and young adulthood (Entringer et al. 2009; DeSantis et al. 2015). For example, Thayer and Kuzawa (2009) reported that in a sample of ethnically diverse pregnant mothers living in Auckland, New Zealand, women who reported higher levels of self-reported ethnic discrimination during pregnancy, on average, had infants who exhibited greater levels of cortisol reactivity in response to a vaccination. Additionally, greater self-reported stressful events during pregnancy predicted significantly lower cortisol concentrations in response to a pharmacological stimulation test in prenatally stressed young adult children (Entringer et al. 2009). Thus, early evidence suggests that greater severity of maternal prenatal stress and trauma may cause durable increases in physiological stress reactivity

into adulthood and increase one's risk of developing a wide range of psychopathologies (Heim et al. 2019; Krontira et al. 2020; Markham & Koening 2011; McLaughlinn et al. 2010; Monk et al. 2019; O'Donnell & Meaney 2017). In summary, early life exposures during prenatal development may have durable impacts on the function and responsivity of fetal stress physiological mechanisms such as the cortisol-producing HPA axis, and in turn, may also shape postnatal glucocorticoid activity across one's lifecourse.

Ethical considerations limit human prenatal stress research on observational and naturalistic experiments, which have included exposures to acute and chronic stressors (i.e. general life stress, discrimination, flood), psychiatric disease such as anxiety and depression, and major traumatic events including the September 11 attacks in the United States or the Holocaust. As previously mentioned, studies on the long-term psychological and biological effects of prenatal stress are severely limited as participants become older, especially after young adulthood. Though the very small handful of adult studies conducted have displayed mixed results, an overall positive association can be traced (Buchmann et al. 2014; DeSantis et al. 2015; Entringer et al. 2009; Wüst et al. 2005; Ping et al. 2015).

Generally, prenatal stress exposure across a variety of different stressors is seen to elevate either baseline or stress reactivity levels. For example, Western European young adults whose mothers were exposed to significant psychosocial stress (e.g. relationship conflicts, death of someone close) during pregnancy exhibited an overall higher increase in cortisol response to the Trier Social Stress Test, a laboratory challenge protocol intended to activate the HPA axis as a form of acute stress (Entringer et al. 2009). Additionally, pregnant mothers that experienced the June 2008 Iowa floods gave birth to infants that displayed an average increase in the stress response to brief maternal-infant separation (Ping et al. 2015). This effect was only seen in

females, and the later in gestation the mother experienced this stressor, the greater the cortisol increase. Conversely, it must be noted that some studies reported no changes in offspring stress reactivity after challenged or found decreases in baseline GCs and stress reactivity, but a majority of human studies have reported increases in cortisol levels after stress exposure.

Adult depressive effects of prenatal stress influenced alterations in stress physiology

To review the discussion on stress and HPA axis up to this point, I have described the broad regulatory scope of the HPA axis in human development reflects the widespread downstream and intergenerational impacts on phenotype that are coordinated by cortisol. As stated, much research on the long-term and intergenerational phenotypic consequences of stress-induced HPA axis dysregulation has consistently reported impacts on birth outcomes and future mental health status. Three separate meta-analyses concluded that various forms of gestational stress (e.g. psychosocial stress, domestic violence, maternal anxiety) predict shorter offspring gestational age, greater risk for preterm birth, and lower offspring birthweights (Bussières et al. 2015; Ding et al. 2014; Shah et al. 2010). Additionally, the long-term consequences of adverse birth outcomes, mainly low birthweight, has shown to impact adult HPA axis dysregulation (G2) (Lahti et al. 2005; Lee et al. 2014; Nilsson et al. 2001; Phillips & Jones 2006; Schlotz et al. 2005) and in reproductively aged women, influence the intrauterine environment and future developing fetus. This work thus points to the potential for early stressors to have effects that transcend the exposed generation to impact fetal development in the next generation.

The HPA axis has also been implicated as a possible mechanism underlying the effects of prenatal (Van den Bergh et al. 2008; Halligan et al. 2004; Weinstock 2008) and early life stress (Heim & Binder 2012; Juruena 2014; Tyrka et al. 2008b) on adult mental illness. Studies have

reported associations between greater early life postnatal stress and altered adult HPA axis function across the lifecourse (Fogelman & Canli 2018). For example, in one study, depressed men with histories of child abuse exhibited greater peak cortisol levels after a laboratory stressor compared to non-depressed men abused in childhood (Heim et al. 2008). Early life stressed individuals tend to exhibit greater HPA axis activity in response to acute stressors (i.e. vaccination, first day of school, visual stimuli, etc.) in both early childhood (Gutteling et al. 2005; Ping et al. 2015; Tarullo & Gunnar 2006) and adults (Pesonen et al. 2010; Schalinksi et al. 2015; Vaccarino et al. 2015). Similar long-term impacts on HPA axis function and mental health are seen as a result of prenatal stress, yet the existing evidence is quite limited and only a small handful of studies that assessed adult offspring HPA axis function exist. One of these studies found that women who experienced greater maternal anxiety during pregnancy were more likely to have children with flatted diurnal slopes, an indicator of HPA axis dysregulation, which predicted depression in female adolescents (Van den Bergh et al. 2008). An overwhelming majority of human studies on prenatal and early life stress, however, have relied almost exclusively on self-reported retrospective-recall measures, which are prone to numerous cognitive biases (e.g. recency effect, availability heuristic) and undermined by memory loss and current emotional states (Entringer et al. 2015; Wadhwa et al. 2011). These major limitations emphasize the importance of direct measurement of experience and prospective studies to accurately examine the long-term effects of early life stress.

The following model represents the intergenerational transmission of poor health operating through the reciprocal effects of a stressful intrauterine environment on future adult mental health and biology, and adult mental health and biology among females on a stressful intrauterine environment in the next generation. This model suggests a multigenerational effect

of stress transmission that manifests from the grandmother's experience while pregnant to her future grandchildren.

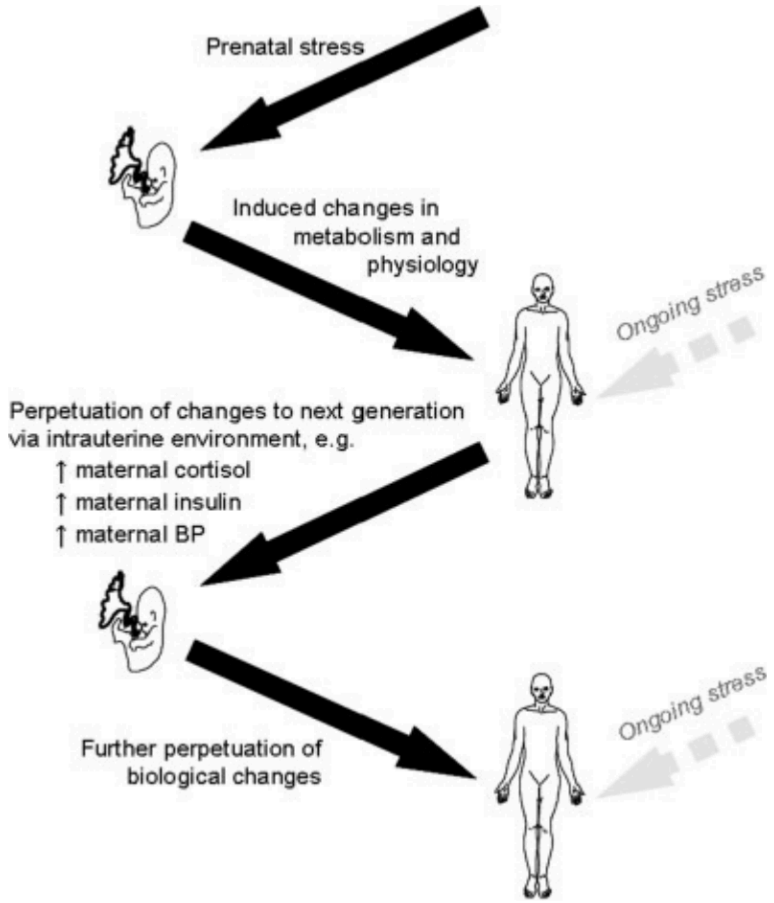


Figure 6. Model of the intergenerational transmission of disease states (Kuzawa & Sweet 2009)

The HPA axis as a potential multi-generational conduit for environmental information

This model of multigenerational transmission of stress may be viewed as beginning with fetal exposure to high circulating maternal cortisol levels due to maternal stress (Cottrell & Seckl 2009). While the influence of maternal cortisol is reduced by the activity of the placental enzyme

11β-hydroxysteroid dehydrogenase (11β-HSD2), elevated maternal stress has been shown to downregulate enzymatic activity in the placenta, increasing maternal cortisol transfer across the placenta (Mairesse et al. 2007). The impacts of maternal stress (G1) on the fetus (G2) are already noticeable during gestation and shortly thereafter, which include fetal growth restriction and preterm birth (Wadhwa et al. 1993; Sandman et al. 1997). Furthermore, maternal prenatal stress predicts offspring HPA axis reactivity across multiple stages of offspring development, suggesting a "programming" effect of maternal cortisol on fetal HPA axis function (Cottrell & Seckl 2009). Prenatal stress-induced effects on offspring HPA axis reactivity have been documented in young infants, childhood, adolescence, and through retrospective assessments in adults and tend to predict elevated offspring HPA axis function (see Table 1).

This growing area of research is consistent with the larger body of scholarship on the effects of postnatal early life stress (G2), another sensitive period for HPA axis function, which are known to have similar programming effects on the HPA axis across development, extending into adulthood (Gustafsson et al. 2010; Heim & Binder 2012; Taylor et al. 2010). Altered HPA axis function in adult women due to their own prenatal and postnatal exposure to stress, is believed to in turn have the potential to transmit similar effects to their developing offspring in utero (G3), thus creating a multigenerational cycle of stress transmission (Fig. 1). Strong evidence from animal models displays discernable impacts of a variety of grandmaternal prenatal stress on second and third generation phenotypes, such as reduced body size, altered stress reactivity, and depressive-like mood (Drake et al. 2004; Ward et al. 2013). A small handful of human studies documents multigenerational effects of prenatal conditions among grandchildren, but these studies only focus on the impacts of undernutrition and rely on retrospective reporting of experience. No study has prospectively assessed grandmaternal in utero stress and followed

their children and grandchildren, allowing one to trace these effects multigenerationally. Despite much interest in the possibility of multigenerational transmission of stress (Gravlee 2009; Kuzawa & Sweet 2009), this model has not been tested in human populations.

2.8 Summary of gaps in literature

Taken together, research to date points to the plausibility of the hypothesis that prenatal and early life stress will have effects that linger into adulthood, and that these in turn could impact the gestational environment experienced by the next generation. If correct, these pathways would represent an important mechanism of multigenerational developmental plasticity in humans and a potential biosocial pathway for the transmission of health inequality in highly-stressed communities faced with social adversity. This pathway would also illustrate how individuals may be influenced not only by the environments that they experience, but by past ones experienced by mothers and grandmothers. However, to date, no study has directly and prospectively measured early stressors (rather than using adult recall) and traced these multigenerational effects in a population in which prenatal stress was both severe and varied across individuals. Additionally, the degree to which the long-term programming effects of prenatal and early postnatal stressors on adult HPA axis function and mental health are malleable is unknown. Finally, the generalizability of past work on the impacts of prenatal and early life stress has further been limited by a lack of diversity in study samples, particularly in low/middle-income populations where the burden of poor birth outcomes, mental illness, and social adversity are high (Patel 2007; Pike 2005; Vigo et al. 2016).

The proposed study will address these gaps by drawing on a 28-year multi-generational study of a population living in Soweto, South Africa, whose mothers (G1) were first recruited

during the marked political violence of the late apartheid era and have since been followed to the present. To date, no study has assessed grandmaternal in utero stress and its multigenerational impacts on their children and grandchildren in humans using a prospectively design. Additionally, the generalizability of early life stress and mental health studies is limited by the lack diverse study samples particularly in LMICs where the burden of mental illness is the highest. Some of South Africa's largest public health burdens both result from and perpetuate this proposed pathway of intergenerational stress transmission. Approximately 30% of South Africans are expected to experience a mental illness during their life (Herman et al. 2009), and 14% of infants are born preterm (WHO 2019).

These statistics are known to disproportionately impact black South Africans and exist against a dark, violent history of racially charged violence against South Africans of color, particularly black South Africans who make up 80% of the country's population. The economic and political legacies of apartheid continue to the present today, and through the proposed intergenerational pathways of stress transmission, the lasting impacts of apartheid may potentially continue to reverberate through the bodies of future generations of black South Africans and sustain the racial health disparities in mental illness and poor birth outcomes that are seen today.

2.9 Aims & Hypotheses

Aim 1: Examine the relationship between maternal prenatal exposure to stress in the first trimester and infant birth outcomes

H1. Birthweight: Greater prenatal stress during the first trimester will predict lower birthweight

Aim 2: Examine the relationship between maternal prenatal exposure to apartheid-related stress and late adolescent mental health.

H2. Mental health: Greater prenatal exposure to apartheid-related stress (G1) will predict greater severity of adult psychiatric risk in late adolescents (G2).

Aim 3: Examine the effect of early life family stress on adult diurnal cortisol rhythms and depression symptomatology

H3a. Mental health: Greater early life stress will relate to greater severity of adult depressive symptoms

H3b. HPA axis function: Greater early life stress will relate to greater adult HPA axis dysregulation and will shape the relationship between early life stress and adult depression

CHAPTER 3: Methodology and Birth to Twenty ("Mandela's Children")

This chapter describes the various methodologies employed to conduct my dissertation research. I first provide a condensed timeline of my research activities, which range from June 2017 to September 2020, and then describe the preliminary fieldwork and formative research conducted to develop the study, which was named the "Soweto Stress Study" (SSS, or "triple S"). I then describe each component of data collection for SSS, which begins with the administrative groundwork and ends with data analysis and dissemination of research findings. As noted in my Introduction chapter, the COVID-19 pandemic prevented me from completing my initial study with the Birth to Twenty cohort, which aimed to examine the intergenerational impacts of prenatal stress from apartheid on HPA axis function and mental health outcomes in the second and third generations. Instead, I present three separate secondary analyses using data from three longitudinal birth cohort studies - two based in Soweto, South Africa and one in Cebu, Philippines - to assess the long-term impacts of prenatal and early life stress on birth outcomes, mental health, and HPA axis function between infancy and young adulthood. Despite the shift in my dissertation project, I will describe the methods used to launch and conduct my initial dissertation research.

Table 1. Timeline of Research Activities

Month	**Activities**
July 2019	Completed IRB approval process; Obtain visa
September 2019	Arrived in Johannesburg
	Interviewed and trained research assistants
October 2019	Began piloting surveys and cortisol collection materials
	Procured study materials
January 2020	Collected data - surveys, salivary cortisol collection
March 2020	COVID-19 pandemic in South Africa, national lockdown begins
	Launched data collection on mental health impacts of COVID-19 study

3.1 Historical, political, and cultural perspectives of South Africa

Pre-colonial and colonial South Africa: an overview

Prehistorical records that trace back to the geographic areas that are present-day South Africa suggest that the land inside the country's borders were important sites for the study and our understanding of human evolution. One of the earliest known hominid species, *Australopithecus africanus*, is estimated to have inhabited the current landmass of South Africa somewhere between 3.67 to 2 million years ago in the Middle Pliocene to Early Pleistocene. The first known example of *A. africanus* was the 2.51 million year old Taung child skull found in 1924. Other hominid species would eventually be found across South Africa, including *Paranthropus robustus* (or *Australopithecus robustus*) (c. 2 - 0.6 million years ago) in 1938.

Australopithecus sebida (c. 2.36 - 1.5 million years ago) in 2008, and most recently *Homo naledi* (c. 335,000–236,000 years ago), all found in the Cradle of Humankind.

The earliest known human populations to inhabit present-day South Africa were the San and Khoikhoi groups, the former a hunter-gatherer society and the latter a pastoral herding society - together known as the Khoisan (Beinhart 2001). Archaeological, historical, and anthropological records suggest that the Khoisan culture existed in South Africa approximately 2,000 years ago in present-day Western Cape (Barnard 2008). As part of the Bantu migration, a major state would emerge in present-day South Africa, known as the Kingdom of Mapungubwe (c.1075–c.1220). Two major Bantu cultural and language groups extending from the Kingdom are known to have existed before the first colonial encounter in 1652: Sotho-Tswana languages (including Sepedi, Sesotho, and Tswana) and Nguni languages (including Setswana, isiXhosa, isiZulu, siSwati, and Southern Ndebele (Beinhart 2001). South Africa's first colonial encounter was in 1488 when Portuguese colonist Bartolomeu Dias made contact with the coastline, eventually reaching the southernmost point of the country, known today as the Cape of Good Hope. The first permanent settlement began in 1652 by the Dutch East Indian Company (VOC) in the Cape (Beinhart 2001). A series of violent encounters between white Dutch colonists and Khoikhoi communities over land ownership escalated into the first Khoikhoi-Dutch War in 1659, which resulted in the eventual expulsion of the Khoikhoi out the Cape Peninsula and a disastrous smallpox epidemic brought by Dutch settlers.

The violent establishment of the Dutch settlement continued throughout the 18th century when settler colonial management of various global Dutch colonies imported slaves from present day Malaysia, Indonesia, Madagascar, and Mozambique. Smaller, additional groups of Europeans came to the Dutch "Cape Colony" including independent Dutch settlers not part of the

Dutch East Indian Company and French protestants fleeing religious persecution (Beinhart 2001). The early historical roots of present-day systems of race in South Africa are understood to partly derive from this period of Cape Colony history, where white supremacist societal hierarchies among slaves, indentured servants, workers, indigenous Africans, communities from diverse ethnicities, and white European settlers formed. The Dutch settlers became known as "Boers" meaning farmer in Dutch and Afrikaans, the eventual language of Boer descendants and present-day ethnicity in South Africa. Around this time, a growing population of Griqua people, or a group of ethically and culturally diverse people who were descendants of sexual relations and violence between European colonists, Khoikhoi, and slaves (Beinhart 2001). These people would eventually be categorized under the "Coloured" racial category in apartheid South Africa. Mass migrations known as the Great Trek took place where working class Boers of the VOC fled inward into the interior of South Africa (Figure 1).

Figure 1. A map of the expansion of the Trekboers (1700–1800)

After the British seized the Cape in 1795 to prevent French possession of the colony. During this time, a major clan of the larger Nguni communities called the Zulu would gain significant political power. The Zulu kingdom became a power state under the leadership of Shaka kaSenzangakhona, also known as Shaka Zulu, who would lead a mass expansion into the regions north of present day KwaZulu-Natal in the east coast (Beinhart 2001). Forced expansion from the Zulu kingdom initiated what is known as the Mfecane, a period of widespread chaos and warfare among indigenous communities across southern African between 1815-1840. The Mfecane displaced various African clans from their lands to other regions across southern Africa, which precipitated continued violence against African clans. The Zulus would continue to grow in power and face intense militarized battles against European colonists into the late 19th century until their ultimate absorption into the British colony of Natal in 1897.

Colonial possession of various areas of South Africa would vacillate between the British and Dutch between the late 1700s to early 1960s. Another major development in the formation of "race" in South Africa was through land legislations during the first half of the 1900s. British colonists instituted the 1913 Natives Land Act, which divided 87% of the land to "whites" and 13% to "Africans." The formation and ownership of "private property" became a tool to rob Africans of their land (Beinhart 2001). And while many Africans lived on white owned land, their social standings were stripped of power and minimized to slave labor. In 1961, the British gained considerable political power after a rise of Afrikaner republicanism, which was characterized by the election of the Afrikaner-led National Party (NP) (Beinhart 2001). The NP and its leaders, D.F. Malan, J G Strijdom, and Hendrik Verwoerd, all white Afrikaner male political leaders. The rise of the Afrikaner NP saw with it the end of the British-led Union of South Africa and the formation of the NP-led Republic of South Africa (Figure 2). This

transition would facilitate the rise of racial segregationist laws, which developed during British and Dutch colonial rule and included informal segregation, formal legislation (e.g. Native Location Act of 1879), and the creation of the pass laws (Beinhart 2001). Various sets of legislation rapidly concretized the system of "grand apartheid," or the systemic separation of "races," which were artificial social categories for organizing the four differential "racial groups" of South Africa: Black, Coloured, Indian, and White.

The first set of apartheid laws prohibited marriage and sexual relations across "racial" lines (Prohibition of Mixed Marriages Act of 1949 and the Immorality Amendment Act of 1950), produced the social technology of "racial" classification (Population Registration Act of 1950) along with sub-classifications. These policies created political reasons and formal legislations to control and disenfranchise non-white people in the Republic.

An introduction to the history and racial capitalism of Apartheid

The South African *Apartheid* (an Afrikaans word meaning "separateness", "the state of being apart", or literally "apart-hood") regime introduced in 1948 manufactured a nationally institutionalized system of racial management and socioeconomic inequity. This system of social stratification, upheld by authoritarian political powers of *baasskap* (literally as "boss-ship" or "boss-hood" in Afrikaans, or "white supremacy" in English), concretized the political, social, and economic domination of South Africa by the country's white minority population. South African apartheid is understood to operate as a highly successful and systematized form of what is known as racial capitalism. Black Studies professor Cedric Robinson coined the term in his 1983 book titled *Black Marxism: The Making of the Black Radical Tradition*, as described below.

> “Racism, I maintain, was not simply a convention for ordering the relations of European to non-European peoples but has its genesis in the "internal" relations of European peoples. As part of the inventory of Western civilization it would reverberate within and without, transferring its toll from the past to the present. In contradistinction to Marx's and Engels's expectations that bourgeois society would rationalize social relations and demystify social consciousness, the obverse occurred. The development, organization, and expansion of capitalist society pursued essentially racial directions, so too did social ideology. As a material force, then, it could be expected that racialism would inevitably permeate the social structures emergent from capitalism. I have used the term "*racial capitalism*" (emphasis added) to refer to this development and to the subsequent structure as a historical agency” (Robinson 1983:2).

In other words, the economic system that thrives on the persistent accumulation, increasing rate of capital accumulation and control of the means of production and profit, known as capitalism, "can only accumulate by producing and moving through relations of severe inequality among human groups” and sustain itself through "unequal differentiation of human value” (Melamed 2015:76-85). Robinson (1983) argues that since the 17th century, "the development, organization, and expansion of capitalist society pursued essentially racial directions" - mainly skin color, phenotype, and ethnic identity, and that "it could be expected that racialism would inevitably permeate the social structures emergent from capitalism.” Apartheid is a prime example of a racial capitalist system, one not unlike American, European, and other non-Western and South Africa systems of capitalism, which generated and continues to generate enormous amounts of profit from a wide range of industries - most significantly, mineral mining,

agriculture, steel, electricity, and service. This racial capitalist system maximized disposable labor from Black communities, migrant communities, and communities of color and limiting their opportunities for social mobility, education, and socioeconomic development, and in turn, optimizing the modes of production to sustain their profit accumulation and power (Crais & McClendon 2013; Melamed 2015; Robinson 1983).

The NP continued to impelment a series of legistations to institutionalize apartheid laws, but growing resistance movements against the apartheid regime began to emerge throughout the 20th century into the next century. The apartheid government created legislations to demobilize opposition movements (e.g. Suppression of Communism Act of 1950), developed autonomous, segregated governments for "Blacks" known as bantustans, and also coordinated a countrywide forced removal system that attempted to segregate the country's population into 20 bantustans, also known as the "homelands." Apartheid continued to grow into the second half of the 20th century. This included limited distribution of passes to limit the number of non-whites in the cities, harsh enforcement of pass laws, unequal distribution of resources such as hospitals, quality residential spaces, and other public services, union busting, laws prohibiting use of public and white-owned spaces, poor educational facilities, very limited work and social opportunities for women, among many other oppressive conditions.

A wide diversity of resistance movements with a range of organizing strategies, from peaceful protests to militarized civilian insurgencies, emerged shortly after the institutionalization of apartheid in 1948. A series of pro-Black and -African organizing groups, who would eventually become major political parties in the country, built a critical mass and power in their bases. These included parties such as the African National Congress, the currently ruling party in South Africa; the Pan Africanist Congress, a branch off of the the ANC that

encouraged multiracial liberation rather than ANC's focus on Black nationalism; the Black Consciousness Movement, motivated by the Black Power movement in the United States and initially started by an educated leadership; the numerous student movements; trade unions and religious institutions; specific race- and ethnicity-based resistance groups (e.g. Jewish, Indian, Coloured, etc.); and later, international allies, which eventually motivated the global boycott against the South African government. One of the most pivotal moments of resistance in the history of apartheid is based in Soweto, a major Black township of Johannesburg.

Figure 2. A map of South Africa (Britannica 2020)

Soweto (a portmanteau of "Southwestern Townships") began as an amalgamation of separate townships in the southwest region of Johannesburg. After the discovery of gold in Johannesburg (also known as the "City of Gold") in the mid-19th century, the Dutch/Afrikans-led "South African Republic" created a brickmaking industry in present-day Soweto because of the large quantity of naturally available clay. Overtime, working class communities of all "racial" groups settled in the area until population management laws resegregated South African communities, which is when the concept of the "township" became popularized (Seekings & Nattrass 2005). Overtime, Black communities emerged in the various townships that make up Soweto but the history of social life in the years preceding apartheid up until decolonization includes increasing cases of government divestment, informal settlements, mass migration, growing unplanned urbanization, deep political organizing and resistance, and state violence (Bonner & Segal 1998). Soweto was eventually resegregated again geographically but this time by language groups, which was frequently used synonymously as ethnic categories (e.g. Sotho, Tswana, Tsonga, Venda, Zulu, Xhosa, etc.) (Bonner & Segal 1998).

Soweto became a site of immense cultural and historical significance in the struggle against apartheid, particularly after June 16, 1976 when the Soweto uprising took place. After the colonial government enforced all public education in Afrikaans rather than the native African languages, posing a major barrier to educational attainment and social mobility and a deliberate attempt to stymie the growth of African communities, an estimated 20,000 students protested in Orlando West marching from Naledi High School to Orlando Stadium. Police open-fired on thousands of youth, resulting in 176 deaths including Hector Pieterson, a twelve-year old South African student (Harrison 1983). Emergency clinics at local clinics and hospitals, including Chris Hani Baragwanath Academic Hospital, a major tertiary hospital in the Diepkloof area of Soweto

and the site of this dissertation research, overflowed with injured children (Ndlovu 2006). The uprising had a far-reaching ripple effect, motivating other riots and solidarity marches in Johannesburg, other Black townships, places of employment, and localities across the world (Beinhart 2001; Ndlovu 2006). International bodies such as the United Nations condemned the state-sanctioned attack (Harrison 1983). The Soweto Uprising was one of a series of many events during the late 1970s to democracy in 1994 that mobilized local, national, and international bodies to resist the apartheid regime. These included the United Nations, the Commonwealth, numerous world governments, transnational bodies, an international academic boycott (including the American Anthropological Association) (Paris & Gallin 1977), and even the International Olympic Committee. By the 1980s, the apartheid government faced chronic precarity due to nearly insurmountable pressure within and outside its borders.

The dissolution of the apartheid regime in South Africa finally came between the late 1980s to early 1990s. Black townships were central sites of violent resistance between the anti-apartheid struggle and the Pieter Willem Botha administration, the Prime Minister and staunch supporter of the apartheid regime. Botha declared a state of emergency between 1985-1990 to respond to the dramatic rise in the people's organizing against local authorities, representatives, and leaders of the government. Violent and unchecked social sanctions were implemented both informally within neighborhoods and formally, yet haphazardly, through the government. Government authorities, including the police and military, were provided great jurisdiction to oversee violent tactics for political repression, and overtime, the Republic instituted draconian and facist policies, such as detention without trial, censorship, torture, and murder (Beinnart 2001; Crais & McClendon 2013; McKendrick & Hoffmann 1990). This five year period of political unrest was fueled by continual repression of resistance movements, undercover

government ploys to instigate interethnic violence in Black communities, particularly in hostels, and community-wide violence over scarce resources in townships and informal settlements (Beinhart 2001). It is estimated that approximately half the people who died due to political violence during the apartheid regime died in the last four years (1990-1994) (Beinhart 2001; Hickel 2015). Twenty years before the beginning of the transitional period into democracy was largely characterized by ANC and IFP political violence, which has been described as low grade war (SAHO 2020). I provide an excerpt from my field notes from an interview with a Birth to Twenty study participant who was pregnant at the time of these conditions of political violence:

> Xoli remembers how hard living in the 1990s was. She remembers that the township was divided by the languages that people spoke. There were Zulu sections, Xhosa sections, Tsonga sections, etc. Her husband owned a taxi, and speaking Zulu made people suspect they belonged to the Inkatha Freedom Party (IFP) - a Zulu-led political party that colluded with the NP and even a Afrikaner nationalist and white supremacist organization called the *Afrikaner Weerstandsbeweging* (or the Afrikaner Resistance Movement). When her husband came back from work, he would sometimes have to leave his taxi somewhere and walk home for his own safety. Being a taxi owner and Zulu he was read by others as a possible IFP supporter. He also had "taxi wars" to worry about, or conflicts with other taxi drivers typically over competition for business.
>
> Inkatha used to fight against the ANC, Xoli explained, and they would shoot each other. Other people were burned, including her own cousin, who was burned alive in an open field. Her family was only able to recognize them by their sneakers, as the cousin was

> burned beyond recognition. After this happened, she went to stay with her domestic worker mother at Bezvalley, where she worked. She had given up hope and believed that everyone would die. Her mother was pressured by her employers to vote for a white person, who told her that she should never make the mistake of voting for a black person because if a black person came into political power, there would be severe poverty.
>
> The employer owned a steel company, and when Mandela won the election, the employer's family left South Africa and closed down their steel company. She went to work with the company overseas in 1991 and came back in 1993 to prepare for her marriage in 1994. The bride's ceremony was in 1994 and the groom's ceremony took place in 1995 (Field notes, August 7, 2020).

A series of negotiations between the ANC and the apartheid government began at President F.W. de Klerk's residence in Cape Town on May 4, 1990. The Convention for a Democratic South Africa (CODESA), a coalition of 92 organizations signed a Declaration of Intent that signals support for a "united, democratic, non-racial, and non-sexist state in which sovereign authority is exercised over the whole of its territory" (Welsh 2010:434). The meeting represented the first multilateral and multiracial negotiation to end apartheid in South Africa. A second round of CODESA-led negotiations in mid-1992 took place but was ultimately thrarted by the apartheid government's potential involvement in coordinating police raids in townships and a series of growing conflicts between the ANC and NP. Later, the Multiparty Negotiating Forum commenced on April 1, 1993, which brought a wider range of parties to the table, including far-left and far-right groups. These negotiations eventually facilitated the organization

of the first democratic elections in South Africa's difficult, violent, and tenacious history. The election is widely seen as the end of the apartheid regime.

Despite the countrywide celebration for the election of Nelson Mandela and the actualization of the "rainbow nation," political violence continued to ensue. A new set of national politics unravelled across the country. The new constitution was implemented and the Truth and Reconciliation Council was established to facilitate a national-level restorative justice process that aimed to bear witness to some of the most atrocious violations of human rights during the apartheid regime, speak to the perpetrators of violence, grieve, and transition to a free South Africa (Beinart 2001).

The Birth to Twenty (BT20) study

Nested in a major urban neighborhood of Soweto (FIgure 3) in the largest hospital in the southern hemisphere, the Birth to Twenty study launched in mid-1990 to evaluate the impacts of urbanization, changing social conditions, and larger social environments due to apartheid (Radin & Cameron 2012). Birth to Twenty is a birth cohort study that tracked the development of 3,273 newborn infants (Richter et al. 2007). Mothers and newborns were recruited between 23 April to 9 June 1990 at Chris Hani Baragwanath Academic Hospital (CHBAH or 'Baragwanath'). The founders of the study began data collection unbeknownst to the fact that the apartheid government would eventually topple soon after data collection. Thus, the first cohort of BT20 children unexpectedly became the first generation born into a democratic South Africa as the regime dissolved in 1991.

During the first round of data collection in 1990, pregnant mothers completed a suite of demographic, household, and health-related surveys, one of which included a 16-item survey on

stressful and traumatic life experiences during their pregnancy, which is the major exposure variable of my dissertation examining the long-term lifecourse impacts of prenatal stress. Since the inception of the study, Birth to Twenty has continued data collection almost every year up until today. As Africa's largest and longest running study of its kind, BT20 provides the only dataset in South Africa to study the generational impact of apartheid on health and physiology among black South African communities. Throughout the BT20 study, regular contact with respondents and their families was maintained, promoting retention in the study such that DPHRU are still currently in contact with 1700 original participants, which is quite similar to the attrition rates seen in other longitudinal birth cohort studies in LMICs (Norris et al. 2007).

Today, the study is housed under the Developmental Pathways for Health Research Unit (DPHRU), a research unit jointly funded and sponsored by the South African Medical Research Council and the Faculty of Health Sciences at the University of the Witwatersrand. Birth to Twenty continues to be based in the campus of Baragwanath Hospital in the Diepkloof neighborhood of Soweto, South Africa (Adair et al. 2011; Richter et al. 2007; Richter et al. 2012). Soweto continues to be an ethnically and linguistically diverse community, but overtime has seen considerable class diversity, a growing middle class, and a dynamic peri-urban township (Alexander et al. 2013). Families have also moved out of Soweto, mostly into Johannesburg but also other areas in Gauteng and outside of the province (Norris et al. 2007; Richter et al. 2007). Nevertheless, BT20 continues to work with their longstanding relationships with BT20, now in the third generation, to understand the developmental and lifecourse predictors of health and disease.

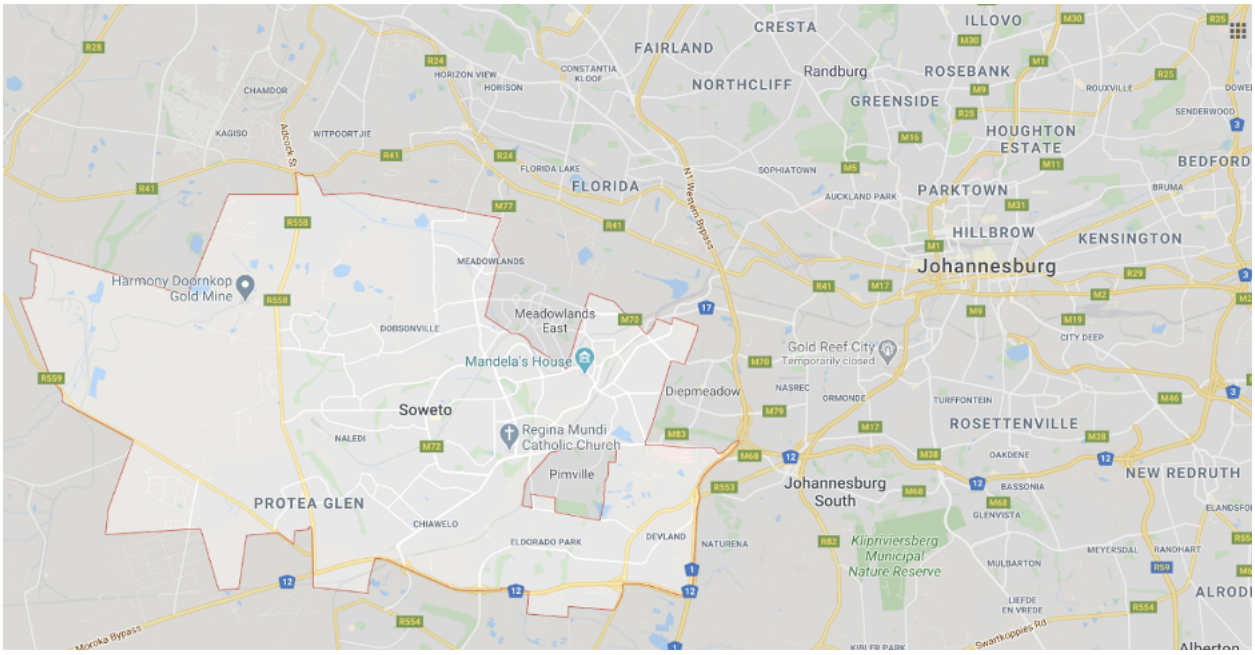


Figure 3. Map of Soweto and Johannesburg

3.2 Data collection

Formative Research (June 2017-November 2019)

I conducted six months of discontiguous formative research at DPHRU in Soweto during June-September 2017, June-August 2018, and January 2019. During these field experiences, I familiarized myself with the research unit, the available datasets and ongoing studies, data collection platforms and systems, and team culture. I also learned about the social, political, economic, and cultural conditions in Soweto and Johannesburg that gave me critical insight into the contexts of mental health in Soweto. Overtime, I developed a strong collaborative relationship with DPHRU, worked on secondary data analyses throughout my time at Northwestern (Chapters 4 and 5), and prepared to launch data collection for the Soweto Stress Study in August-November 2019. Research ethics approval was obtained for both waves of the

study from the Institutional Review Board Office and Northwestern University and the Human Research Ethics Committee at the University of the Witwatersrand.

Wave 1 - Ethnography

This study consisted of two waves. Wave 1 (n = 80) investigated the social, political, and ethnographic perspectives on mental illness in the context of a post-apartheid South Africa to explore perceptions of generational trauma, resilience, healing, and justice. Wave 2 (n = 250 mother/child pairs) used existing survey data, new data, and sample collection to test the lifecourse and intergenerational effects of early life stress experienced by now young-adult mothers.

Wave 1 participants included 1) medical professionals and other professionals in mental healthcare and mental health-related fields; 2) mental illness patients diagnosed with and/or actively experiencing depression, anxiety, post-traumatic stress disorder, and a culturally-relevant form of mental dysfunction and their caregivers, 3) lay individuals. English-speaking participants above the age of 18 will be interviewed and examined through participant-observation. This study did not include individuals who were: unable to consent, pregnant women, cognitively impaired, prisoners, and other detained individuals.

Semi-structured interviewing

Recruitment for lay people, medical professionals, and key informants: I used a convenience (e.g. friends, extended social network, new acquaintances met at public events) and snowball sampling strategy to interview adults in Soweto to understand everyday perspectives on stress, trauma, mental illness, and well-being. Extensive field notes were taken during and

immediately after the interview. Field notes were elaborated and edited after completion of the interviews and some time for reflection. All interviews were confidential, anonymous, and recorded after receiving informed consent. Recordings were then transcribed and translated, if needed.

Participant-observation

To understand conceptions of intergenerational risk, trauma, resilience, and mental illness, I conducted participant-observation to understand, interpret, and analyze daily life as a way to understand emic views of these concepts. My major sites of ethnographic observation were DPHRU at Baragwanath Hospital, the Diepkloof neighborhood of Soweto, a major mental health NGO and counselling-based call center, two public tertiary public hospitals in Johannesburg, the northern suburbs of Johannesburg, and the Soweto-Johannesburg region at large. I took regular field notes after conversations, site visits, interactions, etc. and wrote reflective observations about these and past events from my ethnography.

Data analysis

Interview data and field notes were first organized for clarity. Transcribed recordings were uploaded to Dedoose, a qualitative data analysis software, and coded using a codebook. To create the codebook, I reviewed all field notes from my interviews and identified overlapping and noteworthy themes. Once these themes were identified, I created a code book based on the relevance, salience, frequency of the codes from this preliminary analysis. I then coded the transcripts using the codebook and flexibly editing the codebook if needed. All interviews were then coded and major themes from across the transcripts were identified. Coded data were then

compiled based on themes or sub-themes and thematically analyzed to identify how people made sense of mental health, intergenerational trauma, and apartheid.

Wave 2: Soweto Stress Study (SSS)

Before conducting any data collection, I first coordinated the discussion, review, and negotiation of two major contracts for this international study. These included the Material Transfer Agreement to allow me to ship biological samples overseas, and the Research Collaboration Agreement which clarifies NU-Wits policies on intellectual property, publishing rights, data sharing, finances, etc. I also worked closely with the administrative team at DPHRU to prepare the financial, logistical, and data management components of my project and to ensure a successful project launch.

Piloting

All survey materials and new biological sample protocols were piloted before formal data collection ensued. The survey pack was finalized and compiled in July 2019 and distributed to five research assistants at DPHRU with expert proficiency in the primary African languages spoken in Soweto - isiZulu, isiXhosa, isiSotho, and isiTsonga. The daily diaries administered during the home cortisol collection, which included morning and evening surveys for both adult and child and a health questionnaire for the adult, were also piloted. The following instructions were provided to each RA:

1) Read through questions in English and note if any questions, responses, or instructions do not make sense on the yellow pages (yellow pages were inserted in between each survey for notes);

2) Read through questions in your home language and follow the same directions as Step 1. Also, please make any changes, recommendations, or suggest new words/phrases in your home language. More the better;

3) Read through questions in your second most proficient African language and follow the same directions as Step 2.

All comments were compiled into one survey pack and questions were adapted accordingly. Any conflicting edits were reviewed with at least one of the five RAs for further clarification. Most edits focused on unfamiliar or uncommon words or phrases in English and when translated into their home languages, as well as cultural differences in how certain concepts were described or assessed. Afterwards, a final survey pack was created and uploaded onto REDCap.

The cortisol collection protocol and daily diaries were replicated and adapted from the same methodology used in Dr. Emma Adam's laboratory at Northwestern University (Adam & Kumari 2009). The daily diaries were piloted and adapted along with the survey pack as described above. Complete cortisol collection kits were distributed to two adults and two children between the ages of 5-10 in October 2019. The participants were asked to follow instructions explained by me and provided in the kit, which included collection times for each saliva sample, daily diary instructions, storage information, and precautions against improper collection techniques. The adults were instructed to take notes based on their and their child's

experience with the technique, with a particular emphasis on barriers or inconveniences associated with collection. Afterwards, I reviewed all samples and surveys for adherence to protocol and discussed the participants' experience with the collection method. All comments were summarized and necessary changes in the protocol were made. These included the emphasis of specific steps during the cortisol collection training, the amount of saliva to provide, and clarifications about acceptable storage conditions, among others.

Training of research assistants

Research assistants were hired and trained for the three days preceding data collection. RAs were provided a comprehensive yet thorough overview of the study aims, rationale, and theoretical background, engaged in a discussion about their thoughts on the study, and asked questions. The following day, each measure included in the survey pack was individually reviewed and specific questions that caused confusion during piloting were highlighted and discussed. Afterwards, RAs were trained on administering survey questions and open ended interview questions. Common issues were discussed, such as participant fatigue, confusion over changes in the range of scales, and dealing with uncomfortable questions, and several strategies were provided. The last day, RAs practised administering the questionnaires, the standard operating procedure for assisting a distressed or suicidal participant was reviewed, and all consent forms were examined and administered for practice.

Sample selection and recruitment

While all participants come from the larger Birth to Twenty study, the follow-up subsample recruited 250 mother-child pairs and 100 adult men into Wave 2 of the study or the

"Soweto Stress Study" (SSS). This study sample included 2G adults, both men and women, and 3G children of all genders. Multilingual research assistants (RA) contacted participants using phone-based recruiting, the standard recruitment protocol at BT20 and DPHRU. The following selection criteria were used to select 2G and 3G participants.

Inclusion criteria

2G: Mothers (1G) were enrolled in BT20 during gestation and completed the antenatal stress questionnaire; 2G adult men did not have to have a 3G child to be eligible for the study.

3G: Children of 2G mothers who meet the above 2G criteria; between ages 4-10 years old

Exclusion criteria

SSS did not recruit individuals who were: unable to consent, pregnant women, cognitively impaired, prisoners, and other detained individuals.

Data storage and management

A project inception meeting was organized with the support staff at DPHRU, which included the finance officer, human resources officer, database manager, and facilities manager. In this meeting, all components of the study were reviewed, including the storage and management of data. All survey and biological data were stored onto REDCap (Research Electronic Data Capture), a browser-based online software for data management, survey construction and administration, and workflow methodologies. In the event of internet or REDCap connection problems, paper copies were used for data collection. All paper files, including consent forms, child assent forms, cortisol sample processing files, paper-based survey copies, and daily diaries were organized and filed at DPHRU for future reference and auditing purposes. Data were extracted on a bi-weekly basis for quality control testing, such as identifying

outliers, errors in data entry, missing data, and systematic problems in data capturing. All data were stored in password-protected and/or encrypted storage files or on REDCap and anonymized when transferred to other research staff.

Data extraction

Standard BT20 data extraction protocol was followed. During preliminary fieldwork, data from Birth to Twenty were obtained from the DPHRU data manager after submitting a data request, which included a form and a list of variables, questions, and survey type. Different sections of the data were cleaned at different times in the past depending on the survey.

Data collection

Data collection began on January 13, 2020 at DPHRU in Chris Hani Baragwanath Academic Hospital. Two rooms were allocated to the Soweto Stress Study with one RA in each room. A study team member greeted the participants, explained the study, and received consent before taking anthropometric measurements, including height, weight, mid upper arm circumference, and waist circumference. Seated blood pressure was also collected (protocol described below) and participants then began the survey based questionnaires. Participants were provided a light meal and drink during data collection and were allowed to take as many breaks as desired. Afterwards, RAs instructed the participants on the cortisol collection procedure and daily diary entries. Both the child and adult provided their afternoon samples at this time. Afterwards, the adult participant provided blood droplets for dried blood spot collection. Participants were then compensated (150 ZAR) and released from the study with their cortisol collection kits. A driver picked up their samples 3-5 days after the initial visit and reviewed each

sample with the participant to identify any problems with collection. The driver took notes on each sample and paid the participant an additional 50 ZAR for completing the home cortisol collections.

Participant consent

All participants who agreed to participate provided verbal consent using a consent document that ensures the confidentiality and voluntary nature of the study and emphasizes the potential risks. Written informed consent was not obtained if participants were not literate - for these participants, we obtained written consent. All interviewed were administered by a Zulu and/or Xhosa-speaking research assistant as well as one English-speaking interviewer in a private interview room at DPHRU. The consent process ranged from ten minutes to as long as the participant felt comfortable participating in the study and were fully aware of the risks and benefits involved.

Per the South African National Health Act, which came into effect in March 2012 (Human Sciences Research Council 2012), children between the ages of 7- 18 were required to provide consent through their own assent in addition to receiving permission from their parents to participate. To consent children under the age of 7, we followed the University of Cape Town - Faculty of Health Science guidance, “Research Involving Children” (University of Cape Town 2013). Parental consent and permission were mandatory. During the project, the interviewer monitored children for behavior indicating that they no longer wished to take part such as refusing to cooperate or crying. If a child demonstrated such behavior, the procedures were discontinued. Children were reassured that their participation is not mandatory to ensure that children did not feel coerced to participate.

Anthropometrics

Anthropometric measurements were carried out using World Health Organization standard anthropometry techniques by trained research assistants EXPLAIN. Weight were measured to the nearest 0.01kg and height were measured to the nearest 0.01cm using a stadiometer (Holtain Stadiometer®, Crymych, UK). Waist circumference was measured midway between the lowest rib and the iliac crest, and mid-upper arm circumference measured at the mid-point between the tip of the shoulder and the tip of the elbow using a non-stretchable anthropometric tape.

For adults, obesity was defined as Body Mass Index (BMI) of 30 kg/m^2 or more, overweight is defined as BMI 25-29.99 kg/m^2. For children less than five years of age, overweight will be defined as weight-for-height above two standard deviations (overweight and obese) or above three standard deviations (obese) from the median of the WHO Child Growth Standards. For children aged between 5–19 years, overweight is BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; and obesity is greater than 2 standard deviations above the WHO Growth Reference median. Stunting is derived from WHO age and sex adjusted growth standards and defined as height-for-age z-score below -2 SD.

Road to Health Card

Parents of the BT20 3G participants were asked for their child's Road to Health card (RHC), a medical record summary of a child's health in the first 5 years of life. Information on all South African children's growth, illness and morbidity from birth to the interview are recorded on their RHC. Date of birth, birth weight, available measurements of child height and weight, information on medical history and access to health care services were retrieved.

Survey interview

Upon consent, a series of surveys were administered to collect information on demographics, child and maternal mental health status (depression, anxiety, and PTSD risk), and recent history of child and maternal stress exposures. Surveys were administered by research assistants using tablets and paper copies will be used as back-up materials. The survey interview included the administration of the following instruments:

Table 2. Survey interview questionnaires

Title	Description
Demographics Questionnaire	General survey that assesses various sociodemographic factors, including but not limited to age, sex, race, socioeconomic status, educational attainment, household conditions, access to healthcare, etc.
General Health Questionnaire	Screening device for identifying minor psychiatric disorders in the general population and non-clinical psychiatric settings. Assess four domains of mental health: somatic symptoms, anxiety and insomnia, social dysfunction and severe depression.
General Anxiety Disorder Scale	Short question screening tool evaluating seven symptoms of anxiety for adults.
Post-Traumatic Stress Disorder Checklist	20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD.
Coping Checklist	Survey that assesses prevalence of psychological social, economic, and political factors that shape resilience
Development and Well-Being Assessment	Package of interviews, questionnaires and rating techniques designed to generate ICD-10 and DSM-5 psychiatric diagnoses on 2-17 year olds.

Perceived Stress Scale	Survey that assesses the degree to which situations in one's life are appraised as stressful. Items were designed to query how unpredictable, uncontrollable, and overloaded respondents find their lives.
Perceived Social Support Scale	Survey that assesses the degree to which participants receive, feel, and perceive the ability of social support in their lives.
Life Events Checklist	Survey that catalogues major negative life events that have occurred over the past one year.
Biomarker survey	Survey that records biomarkers including blood pressure and anthropometrics
Semi-structured Life History Interview	A series of open-ended questions designed to explore participants' life experiences. Domains of life examined in this interview include but are not limited to childhood, migration, stress and trauma, apartheid-related experiences, coping and resilience, social support, etc.
Administered at home during the 4-day cortisol collection:	
Health Questionnaire	Survey that assesses health status, disease history, health behaviors, and lifestyle
Morning Daily Diary	Survey that assesses daily stress and mood that occurred between bedtime and morning the next day.
Evening Daily Diary	Survey that assesses daily stress and mood that occurred between morning and before bedtime.

Office blood pressure measurement

Office blood pressure monitors were fitted on the left arm by the research assistant and blood pressure were measured following the 2018 European Society of Hypertension Guidelines after 5 minutes of rest and with the participant seated, feet placed on the floor and legs

uncrossed. With the forearm resting at the level of the heart, three measures will be taken using an appropriate size cuff at the brachial artery on the left arm, with 2 minutes between each measure. A further reading is taken if the first two readings differ by >10mmHg. Systolic and diastolic pressure and pulse will be recorded for all readings. Blood pressure measurements were taken as the average of the last two readings with the first reading discarded. The criteria for referral are resting office blood pressure of 140/90 mmHg or above.

Dried blood spot collection

The participant was first asked to rotate their arms to encourage blood flow to the fingers and which finger they would prefer to receive a lancet stick. The selected finger was sterilized using an alcohol swab then allowed to dry. Afterwards, the hand was rubbed in a downward direction from the palm to the end of the finger, then the selected finger was pricked using a sterile, single-use microlancet (BD Microtainer Contact-activated lancet). The first drop of blood was wiped away using a roll of cotton and each subsequent drop of blood was blotted onto the filter paper (Whatman 903 Protein saver card). The filer paper was dried between 4 and 14 hours (overnight). Cards were then placed in a freezer box at -20C at DPHRU until samples were shipped to the Laboratory for Human Biology Research at Northwestern University in Evanston, IL, USA. C-reactive protein (CRP), a protein biomarker of inflammation, was analyzed to assess inflammatory profiles and HPA axis dysregulation. Only participants above the age of 11 were recruited for dried blood spot collection. No developmental considerations for sampling are necessary for C-reactive protein (CRP), the sole biomarker collected through dried blood spots, as CRP is understood to circulate at stable levels as early as birth (Ng et al. 1997).

Diurnal salivary cortisol and daily diary collection

Daily diary and cortisol collection task: All participants, both parents and children (total age range: 4-31), were invited to participate in a four day cortisol and daily diary collection. The collection involved two activities: 1) collecting saliva samples (starting the evening of the interview to the next three days); 2) completing morning and evening diaries (starting the evening of the interview). For children under the age of 10, parents were asked to assist with sample collection. Participants took these kits home with them to complete. All completed materials will be returned (identified by ID number only) to a DPHRU driver upon completion. All samples were stored in the participant's home refrigerator (if available). If placed in room temperature, participants were instructed to record this.

Morning and evening diaries: Evening diaries were completed the same night and queries events and emotions occurring that day for the upcoming day. Short morning diaries were completed immediately after waking. Morning diaries assessed sleep quality and duration from the night before, and expectations for the upcoming day. To elicit reports of both major and minor stressors, participants were asked to describe the event that was the "most stressful" for them that day, as well as smaller events that were "stressful", "annoying" or "challenging" (they also reported their mood states in response to each of those events). Participants also reported on health behaviors such as smoking, drinking, naps and exercise that day. All participants will complete the Morning Diaries using paper and pencil. All participants were given a back-up set of paper diaries and saliva collection tubes.

Home Cortisol Samples: Participants were asked to provide cortisol samples on the two nights after the interview through passive drool. A total of thirteen samples were collected, which were provided during the times listed: 1) Afternoon (at the interview), 2) Evening of

interview (e.g. before bedtime), 3) Waking, 4) Waking + 30 mins, 5) Waking + 45 mins, 6) Evening 7) Waking, 8) Waking + 30 mins, 9) Waking + 45 mins, 10) Evening, 11) Waking, 12) Waking + 30 mins, 13) Waking + 45 mins. Three additional samples were provided for make-up collections for waking, waking + 30 mins, and waking + 45 mins. Samples were refrigerated immediately after sampling.

Missed diaries/samples and Reminder Calls: If participants missed collection of a diary entry, saliva sample, or sleep measurement on one of the study days, they were asked to "make up" for the missed sample, diary, or sleep measurement on the following days (i.e. we left a 1 day buffer between the diary study completion and dropping off the materials). Research assistants were available by cell phone to answer questions from diary participants.

Delivering Completed Diary Materials: All completed diary study materials were returned to a research assistant from the study at DPHRU by a driver who collected samples at participants' homes. All diary study participants will receive a second 150 ZAR honorarium as an incentive for participation in this portion of the study. Saliva samples were stored at -20C degrees in a locked laboratory at DPHRU until assayed.

CHAPTER 4:
Maternal prenatal stress during the first trimester and infant birthweight in Soweto, South Africa

Abstract

Background: Approximately 14.2% of newborns are estimated to be born low birth weight (LBW) in South Africa. Past work has implicated maternal prenatal stress as a potent predictor of poor birth outcomes, including preterm birth, intrauterine growth restriction, and LBW. However, less is presently known about the impacts of prenatal stress during early gestation in low- and middle-income contexts, where public health burdens due to LBW are much higher.

Objective: We assess the effects of psychosocial stress during the first trimester on birthweight in a large sample of women (n = 657) in Soweto, South Africa, a peri-urban township located in the Greater Johannesburg area.

Methods: Data come from the Soweto First 1000 Days Cohort, a study of maternal and fetal predictors of infant birth outcomes. Multiple regression models were used to examine the impact of prenatal stress on infant birthweight.

Results: The prevalence of LBW was 16.6%. Adjusting for maternal age, gestational age, fetal gender, body mass index, and parity, maternal prenatal stress during the first trimester was a borderline predictor of lower birthweight in this sample ($\beta = 12.7$, $p = 0.071$, 95% CI [-26.4, 1.10]). Women who reported greater levels of stress appeared to have non-significantly longer gestations, and the negative impact of maternal stress on birthweight only appeared after adjusting for this pattern.

Conclusions: These results suggest that fetal growth restriction associated with first trimester maternal stress may contribute to lower birthweights in this sample. Our findings report modest relationships between maternal stress specific to early gestation as likely important to birth outcomes in this urban South African sample.

4.1 Introduction

Being born low birthweight (LBW, BW<2500g at birth) increases one's risk for a wide range of poor physical and mental health outcomes that can persist across the lifecourse, and can even have effects that impact health in the next generation (Barker 1998; Kuzawa & Sweet 2009; Levitt et al. 2000). It is well-known that neonates born small or preterm face greater risk of perinatal morbidity and mortality (Bernstein et al. 2000). Additionally, growing evidence suggests that LBW status also shapes health outcome across development into adulthood, affecting risk of a wide range of diseases such as diabetes (Harder et al. 2007; Whincup et al. 2008), hypertension (Mu et al. 2012), and neuroendocrinological (Jones et al. 2006; Wüst et al. 2005) and inflammatory dysregulation (McDade et al. 2009). In turn, some of the long-term sequelae of being born small can increase the risk of giving birth to lighter babies in the next generation (Kuzawa & Sweet 2009; Thayer et al. 2012). These major public burdens caused by LBW have long impacted low- and middle-income countries (LMICs) at disproportionate levels (UNICEF-WHO 2019), which foreshadows a concerning public health burden caused by the increased risk of diseases associated with both LBW status.

A growing body of research has reported that gestating mothers who experience psychosocial stress are at heightened risk of giving birth to neonates with lower birthweights (Ae-Ngibise et al. 2019; Patil et al. 2020; Therrien et al. 2020; Zhu et al. 2010). Experiences of maternal prenatal stress are understood to contribute to LBW as a result of reduced gestational duration and restricted fetal growth, and often times, a complex combination of both gestational responses. Previous studies have shown that pregnant mothers with greater psychosocial stress tend to give birth to children with shorter gestational ages (Bussières et al. 2015; Coussons-Read 2012), who are preterm (Rosa et al. 2019; Wadhwa et al. 2011; Zhu et al. 2010), who are small-

for-gestational age (SGA) (Class et al. 2011; Khashan et al. 2014), and in some cases, infants who are growth restricted (Berkowitz et al. 2003; Glynn et al. 2001; Resnik 2002). Additionally, previous studies have documented a wide variety of stressors that also predict LBW, which include pregnancy-related stress (Hobel et al. 2008), poverty (Lee & Lim 2010), racial discrimination (Collins et al. 2004), and maternal depression (Grote et al. 2010) and anxiety (Ding et al. 2014). Conversely, some researchers have found no evidence for impacts of stress on birthweight (Engel et al. 2005; Ramchandani et al. 2010).

While the mechanisms underlying the impacts of maternal cortisol on fetal development are only partially understood (Gitau et al. 2001), psychosocial stress exposure during earlier windows of gestation may lead to decreases in birthweight due to neuroendocrine-mediated fetal growth restriction and earlier parturition (D'Anna-Hernandez et al. 2012; Glynn et al. 2001). Three potential mechanisms have been suggested: maternal cortisol exposure through the placenta, downregulation of cortisol-shielding enzymatic mechanisms, and reduced stress reactivity across pregnancy. First, stress-initiated elevations in circulating glucocorticoids (GCs) may lead to greater levels of cortisol to move through the placenta and reach the fetus (O'Donnell et al. 2009). Greater maternal cortisol levels during early periods of pregnancy have been associated with being SGA (Goedhart et al. 2010) and LBW (Bolten et al. 2011; D'Anna-Hernandez et al. 2012; Goedhart et al. 2010). Contrary to the negative feedback loop between adrenal cortisol exposure and hypothalamic corticotropin-releasing hormone (CRH) production, higher cortisol exposure *increases* CRH production in the placenta, which subsequently can upregulate the production of pituitary adrenocorticotropic hormone (ACTH) and in turn, cortisol in both the mother and the fetus (Majzoub & Karalis 1999). Growing evidence also suggests that greater prenatal stress exposure may result in maternal immune dysregulation during pregnancy,

which has been associated with adverse gestational development and birth outcomes, including restricted fetal growth, preterm birth, and LBW (Beijers et al. 2014; Nazzari et al. 2019).

Second, early increases in maternal cortisol during gestation may also downregulate fetal buffering mechanisms against maternal cortisol. Placental levels of 11β-hydroxysteroid dehydrogenase (11β-HSD-2) act as a natural shield against maternal cortisol *in utero* by converting cortisol into biologically inactive cortisone. Maternal cortisol, however, is still able to penetrate the fetus in small amounts particularly when circulating maternal cortisol reaches high concentrations or when 11β-HSD-2 is downregulated (O'Donnell et al. 2012). For instance, recent evidence reports that high levels of maternal GCs can consequently downregulate 11β-HSD-2 production, thus allowing greater passage of GCs, including cortisol, into the womb (O'Donnell et al. 2012). Placental 11β-HSD-2 levels are naturally and relatively low during early gestation (Hobel et al. 2008), and during this time cortisol may more easily pass through the placenta during earlier stages of pregnancy to slow fetal growth rate and shorten GA.

Finally, the impacts of early prenatal stressors on fetal development and birthweight may be heightened as behavioral and biological stress sensitivity decreases among mothers over the course of pregnancy. The sensitivity of both major stress-regulatory systems, the HPA and the sympathetic-adrenal-medullary (SAM) axes, declines as pregnancy advances. For example, mothers in advanced stages of pregnancy show decreased psychological sensitivity (Glynn et al. 2001), HPA axis reactivity (Kammerer et al. 2002; Obel et al. 2005), and decreased blood pressure responses to stress (Nisell et al. 1985) relative to those in earlier stages.

While the mechanisms by which maternal GCs contribute to intrauterine growth restriction and preterm birth are unclear, high levels of stress (Glynn et al. 2001; Lederman et al. 2004) and cortisol during the first trimester have consistently been shown to predict LBW

(Bolten et al. 2011; D'Anna-Hernandez et al. 2012; Goedhart et al. 2010). This stands in contrast to the potential impacts of second or third trimester stress on LBW risk, which may play less of a role compared to first trimester stress due to the relative dampening of stress reactivity among late-stage pregnant women (Glynn et al. 2001; Kammerer et al. 2002) as well as the higher levels of 11β-HSD-2 buffering as pregnancy progresses. Thus, during times of low 11β-HSD-2 buffering, normal psychological and physiological stress reactivity, and high levels of stress-initiated maternal cortisol and placental CRH secretions *in utero*, cortisol may more easily pass through the placenta during the first trimester to affect the developing fetus to possibly slow fetal growth rate and shorten gestational length. We hypothesize that greater exposure to maternal stress during earlier periods of gestation will correspond with lower birthweights.

Notably, studies of prenatal stress and birthweight predominantly draw from samples in North America and Europe (Bussières et al. 2015), which leads to a research bias that overemphasizes psychosocial experiences and social-environmental conditions affecting mothers among high-income, Western populations. Consequently, it also overlooks LMICs that face greater burdens of LBW, such as South Africa where rates of LBW are relatively high (14.2%) and surprisingly close to the rates observed in more poverty-stricken countries in the sub-Saharan region (UNICEF-WHO 2019). In South Africa, LBW is the second leading cause of death in children under 5 years of age (Bradshaw et al. 2003). These trends have been tied to a long history of institutionalized segregation, poverty, and social marginalization characteristic of the apartheid regime, which actively discriminated against people of color, including but not limited to individuals categorized as Black, and continues to affect these communities. To address these gaps, here we examine the timing-specific effects of maternal stress during pregnancy on birthweight in a sample of women living in Soweto, South Africa.

4.2 Methods

Study Setting

This study was nested within a large pregnancy cohort study (Soweto First 1000-Day Cohort; S1000), based in the Developmental Pathways for Health Research Unit in Soweto, South Africa between 2013 and 2016. Under the 1960 Group Areas Act, the apartheid government segregated communities of color to live in demarcated areas, and Soweto was reserved for people classified as Black. Today, Soweto is a large peri-urban area of Johannesburg comprised of ethnically-, linguistically-, socioeconomically-diverse African communities (Alexander et al. 2013).

Overall, S1000 aimed to understand the complex associations between multiple maternal factors and fetal and infant outcomes in an urban African context, and to identify the levers that could optimize maternal and child health within the first the 1000 days; from conception to two years of age. Inclusion criteria were as follows: resident of the greater Soweto area, <20 weeks pregnant and no known diagnosis of epilepsy or diabetes at the time of recruitment, 18 years or older and pregnant with a singleton, naturally conceived pregnancy. A total of 657 women were included in the analytical sample, and 173 women were excluded from the final sample because of missing data for key variables. All women provided written informed consent prior to their inclusion in the pregnancy component of the study. Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (M120524].

Demographic, Health and Socio-Economic Variables

Maternal demographic variables were collected by trained research staff using interviewer-administered questionnaires at the first pregnancy visit (<14 weeks GA) (Table 1). Parity was defined as the number of previous births at a gestational age of 24 weeks or more -

regardless of whether the infant was born alive or was stillborn (0 = no previous births, 1 = one or more previous births). Smoking and/or chewing tobacco was reported at baseline. HIV-status was self-reported at each visit and confirmed using the results recorded in the participant's antenatal clinic card. All HIV-positive participants in this study were receiving antiretrovirals. Household socio-economic status was assessed using an asset index which scored each participant according to the number of assets that they possessed out of a possible 11 (electricity, radio, television, refrigerator, mobile phone, personal computer, bicycle, motorcycle/scooter, car, agricultural land, farm animals). This was based on standard measures used in the Demographic and Health Surveys household questionnaire and has been extensively utilized in this setting (Kagura et al. 2016). Maternal education was defined according to the highest level of completion.

Anthropometry

A wall-mounted Stadiometer (Holtain, UK) was used to measure maternal height to the nearest 1 mm at baseline. Maternal weight was measured to the nearest 0.1 kg at each visit during pregnancy using a digital scale. Weight at recruitment (<14 weeks) was used as a proxy for pre-pregnancy weight and, together with height, was used to calculate maternal body mass index (BMI) (weight (kg)/height (m^2)).

Maternal prenatal stress and social support

A 14-item scale was used to assess stress (including relationship, family, economic, and societal stressors) during recruitment (<14 weeks). Each question records a yes/no response to whether the stressor of question was experienced in the past six months. This scale was developed in previous cohort work in Soweto and is considered a reliable measure of stress (Ramchandani et al. 2010). While each scale assesses retrospective exposures of stress within the

past six months, we treat each time of collection as the approximate time of antenatal stress exposure. Social support was measured using a series of nine questions to identify the absence or presence of instrumental and emotional support, including: people available to help, a confidante, being able to speak to her partner, belonging to a community organisation/ church and having a friend with a baby.

Birth outcomes

Gestational age at delivery (weeks) was calculated as: [duration of pregnancy follow-up (date of delivery – date of baseline ultrasound dating scan) + GA at baseline (days)]. Birthweight was measured by trained research nurses within 24 hours of delivery for 82% of neonates. Where assessment within this window was not possible, measurements were taken within 48 hours.

Statistical analyses

All variables were examined for normal distribution and outliers. Bivariate analyses were conducted between exposure variables, birthweight, and covariates. Covariates were included based on *a priori* knowledge of social, biological, and obstetric risk factors that may potentially confound the relationship between prenatal stress and birthweight. The following variables were considered for inclusion as confounding factors: marital status (single, married), household assets (number of assets owned among the following list of items: electricity, radio, television, refrigerator, mobile phone, personal computer, bicycle, motorcycle/scooter, car, agricultural land, and farm animals), maternal education (last year of education completed), household density (number of inhabitants divided by number of rooms available for sleeping), social support (composite score), alcohol consumption (yes/no), maternal depression (Edinburgh Postnatal Depression Scale) (Cox et al. 1996), maternal anxiety (State-Trait Anxiety Inventory)

(Marteau & Bekker 1992), gestational diabetes (self-reported diagnostic status), and HIV status (self-reported) ($p > 0.10$).

Bivariate analyses were conducted to identify potential confounding variables for inclusion in the final analytic models (Table 2). With the exception of known confounding factors for birthweight, only those that were statistically significant at the 0.1 level were included the final models. Multiple ordinary least squares (OLS) regressions were conducted to examine the impact of prenatal stress on birthweight. Maximum likelihood ratio tests assessed whether the models with the interaction terms were an improvement over the main effects models at $p < 0.15$ for declaring the interaction term significant.

4.3 Results

This study included 657 mother and infants (Table 1). Participants included in the analytical sample were similar to those excluded (n = 173) with respect to first trimester prenatal stress, birthweight, fetal gender, maternal BMI, and GA ($p > 0.05$). Late pregnancy prenatal stress, primiparity, and maternal age were significantly different from those excluded from the sample ($p < 0.05$). Mothers in the analytical sample exhibited slightly lower average levels of stress, reported marginally higher rates of primiparity, and were older by about one year. Fetal gender, maternal age, maternal BMI, primiparity, and GA were significantly associated with birthweight.

Table 3 presents the results of the OLS regression analyses of maternal and fetal factors that predict infant birthweight. The unadjusted model (Model l) predicting birthweight on first trimester prenatal stress, while insignificant, displays a negative relationship as expected. This relationship between prenatal stress and birthweight remains insignificant after adjusting for fetal

gender, maternal age, and maternal BMI (Model 2 & 3). The association between prenatal stress approaches significance (β = -12.4, p = 0.079, 95% CI [-26.3, 1.44]) after controlling for GA, which strongly predicts birthweight and accounts for a large portion of the variation (46%). Finally, prenatal stress remains inversely related to and a modest predictor of birthweight after adjusting for primiparity. A one-point increase in prenatal stress scores corresponded with a -12.7 g decrease in birthweight (β = -12.7, p = 0.071, 95% CI [-26.4, 1.10]). Gender, maternal BMI, GA, and primiparity significantly relate to birthweight and maternal age serves as a modest predictor of birthweight. After adding maternal smoking to the model (Model 7), the effect of prenatal stress strengthens but becomes insignificant. The interaction between prenatal stress and gender was not significant (p = 0.752, 95% CI [-32.1, 23.2]) suggesting that there were no gender differences in the effects of prenatal stress on birthweight in our sample. An identical logistic model predicting LBW was also analyzed and found that the effect of prenatal stress on LBW was non-significant yet trended in the expected direction (p = 0.673, OR = 1.03, 95% CI [0.90, 1.17]).

The effect of first trimester maternal stress on GA was also examined to determine whether shorter gestational periods contributed to lower birthweights. Both unadjusted and fully adjusted models show that the effect of first trimester prenatal stress is not associated with GA (results not shown). Specifically, these analyses also reported a positive but non-significant relationship between maternal stress and GA: women with higher levels of maternal stress during their first trimester seemed to have longer gestations.

4.4 Discussion

We report an inverse relationship between maternal stress severity and infant birthweight: first trimester maternal stress is associated with lower birthweights in our sample of women in Soweto, South Africa. There was also no evidence that the relationship between stress and birthweight was modified by maternal depression, anxiety, and perceived social support. These results point to the importance of the first trimester as an important developmental period for infant birth outcomes.

Previous studies have also reported the inverse relationship between higher first trimester prenatal stress and lower birthweights (Coussons-Read et al. 2012; Dancause et al. 2011; Ryu 2019; Vrijkotte et al. 2009; Zhu et al. 2010). For example, in a large sample of expectant mothers in Hefei, China, self-reported stressful life events that occurred during the first trimester predicted lower birthweights, which were unrelated to stress during the second or third trimester (Zhu et al. 2010). Additionally, in a study of the impacts of a severe ice storm, GA and birthweights were lower among women exposed to the ice storm during early and mid-pregnancy (Dancause et al. 2011). Conversely, a number of studies have also reported no evidence for the effects of first trimester stress on birthweight (Rondó et al. 2003). A wide range of severity and type of maternal stress exposure have been examined in past literature, (e.g. pregnancy-related distress, natural disasters, domestic violence, poverty, trauma, etc.) and the downstream biological pathways linking certain forms of maternal experience and LBW may vary, such as the case of maternal depression (Field et al. 2006). Nevertheless, the larger relationship between maternal prenatal stress that occurred during the first trimester and infant birthweight is consistently documented across study populations.

Our final model (Model 7) also uncovered the deleterious effect of maternal smoking during pregnancy on lowering infant birthweights. While the effect of maternal stress approached significance after controlling for key covariates, the prenatal stress variable became statistically insignificant after including the smoking variable into the model, which itself was not a significant predictor of birthweight. Maternal smoking during pregnancy is a well-known risk factor for LBW (Magee et al. 2004; Steyn et al. 2006) and is understood to lower birthweight through various pathways, including fetal hypoxia (Abel 1980), uterine vasoconstriction (Quigley et al. 1979), and oxidative stress-mediated alterations in placental function (Stone et al. 2014), all of which can contribute to fetal growth restriction. Further analyses indicate that prenatal stress and smoking are collinear with one another (results not shown), suggesting a possible bi-directional relationship between the two variables: smokers may exhibit higher stress levels than non-smokers, or highly stressed women may be more likely to smoke as a coping mechanism (Lobel et al. 2008). Because of this collinearity, our measure of prenatal stress alone may adequately capture the negative impacts of both stress and smoking on infant birthweight.

While GA was a significant and expected predictor of birthweight and accounted for 46% of the variation in our models, contrary to the larger literature (Glynn et al. 2008; Zhu et al. 2010), prenatal stress does not appear to lower birthweight as a result of shortened GA in this sample. Our data reported a positive but statistically insignificant relationship between the severity of stress exposure during early pregnancy and GA. It is only after controlling for gestational duration that the negative association between early prenatal stress and birthweight approaches significance (Model 6). This pattern suggests that fetal growth is likely slowed in relation to first trimester stress, but that this stress-linked delay in fetal growth is masked by non-

significantly longer gestations among women in our sample. The lack of an association between stress and GA may be explained by prior global epidemiological patterns of birth outcomes by location, which show that in high-income countries, the majority of LBW babies are the result of shortened gestation rather than growth restriction (Mattison et al. 2001). In contrast, in LMICs, LBW persists irrespective of GA as well as an increased prevalence of SGA due to environmental and nutritional conditions such as greater infectious disease burden and undernutrition, which compromise maternal metabolism and the overall development of the fetus (Pike 2005).

While the prenatal stress scale was operationalized as a marker of maternal stress at the time of collection, the timing effects may reasonably reflect exposures experienced up to six months prior to data collection as the scale assessed retrospective maternal exposures within the past six months. Because the stress assessment was administered before 14 weeks of pregnancy, the measure may represent experiences up to three to six months before pregnancy. Pre-pregnancy maternal stress has also predicted LBW in past studies (Khashan et al. 2008). In the present study, there is also no evidence for the protective effects of social support as the main effects of social support and the interaction between stress and social support was not significant.

In summary, women who experienced psychosocial stress early in gestation gave birth to modestly lower birthweight babies in our sample of South African mothers and infants. Women who experienced greater levels of stress appeared to have non-significantly longer gestations, and the negative impact of maternal stress on infant birthweight only appeared after adjusting for this pattern. These results suggest that delays in fetal growth associated with first trimester maternal stress may contribute to lowering birthweights in our sample. Our findings emphasize the importance of better understanding the sources of stress experienced among women of

reproductive age in Soweto in order create social interventions aimed at reducing maternal stress, especially early in gestation. Furthermore, this study informs larger public health campaigns, such as earlier antenatal visits, earlier ultrasound screenings, and better monitoring of maternal psychosocial states during pregnancy, designed to ameliorate and prevent the high morbidity of poor birth outcomes across South Africa and other LMICs.

4.5 Tables and Figures

Table 1. Demographic characteristics, social experience, and birth outcomes

Variables	n = 657	Mean (SD)	%	Range
Demographics				
Infant gender (% female)	326		49.6	
Age (at enrollment)		30.1 (5.8)		18 - 44
18-24	142		21.6	
25-29	183		27.9	
30-34	169		25.7	
35-44	163		24.8	
Marital status				
Single	403		61.3	
Married/Cohabiting	254		38.7	
Educational attainment (% attended)				
No school or primary school	17		2.6	
Secondary school	478		72.8	
Professional/teaching/university	162		24.7	
Maternal body-mass index (BMI)	28.2	28.2 (6.22)		15.8 – 60.6
Primiparity (count)				1-9
0	589		89.7	
≥1	68		10.3	
Smoking				
No	602		91.6	
Yes	55		8.4	
Social experience				
Prenatal stress, 1st trimester (count)	4 (2.3)	3.7 (2.3)		0-12
Social support, 1st trimester (count)	6 (1.2)	6.1 (1.3)		2-8
Maternal depression, 1st trimester	9.4 (5.9)	9.4 (5.9)		0-27
Maternal anxiety, 1st trimester	9.4 (2.5)	9.4 (2.5)		6-21
Infant birth outcomes				
Birth weight (g)		2971 (578)		730 – 4500
Low birth weight (<2500g)	109		16.6%	
Gestational age (week)		38.1 (2.4)		25 - 42
Preterm birth	96		14.6%	

Table 2. Zero-order correlations across study variables

	1	2	3	4	5	6	7	8
1. Birthweight	1							
2. Stress	-0.0299	1						
3. Gender	-0.0668	0.0222	1					
4. Maternal age	-0.0749*	0.0122	0.0455	1				
5. Maternal BMI	0.1615*	-0.0142	0.0221	0.1121*	1			
6. Gestational age	0.6822*	0.0346	0.0451	-0.0846*	0.0073	1		
7. Primiparity	-0.0125	-0.0081	0.0331	-0.2654*	-0.1470*	0.1242*	1	
8. Smoking	-0.0719	0.2071*	0.0138	-0.0644	-0.0445	-0.0083	0.0983*	1

*$p < 0.05$

Table 3. Multiple regression models of first trimester prenatal stress scores predicting birthweight (grams)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Prenatal stress	-7.6 ± 10.0	-7.2 ± 10.0	-7.0 ± 9.9	-6.3 ± 9.8	-12.4 ± 7.1^	-12.7 ± 7.0^	-10.3 ± 7.2
Gender (female)		-76.4 ± 45.1^	-72.7 ± 45.0	-76.1 ± 44.4^	-114.1 ± 32.0***	-109.8 ± 31.8**	-109.3 ± 31.8**
Maternal age			-7.1 ± 3.9^	-9.0 ± 3.8*	-3.0 ± 2.8	-5.1 ± 2.8^	-5.3 ± 2.8^
Maternal BMI				16.1 ± 3.6***	15.0 ± 2.6***	14.0 ± 2.6***	13.9 ± 2.6***
Gestational age					23.7 ± 1.0***	24.0 ± 1.0***	24.0 ± 1.0***
Primiparity						-165.7 ± 54.7**	-158.1 ± 54.9**
Smoking							-94.5 ± 59.3
Intercept	2997.5 ± 42.9***	3034.0 ± 47.9***	3244.7 ± 124.1***	2849.1 ± 151.0***	-3658.9 ± 285.7***	-3635.6 ± 284.0***	-3616.1 ± 284.0***
Model R^2	0.0009	0.0053	0.0104	0.0399	0.5034	0.5103	0.5122

^$p < 0.10$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

CHAPTER 5:
Psychological Legacies of Intergenerational Trauma under South African Apartheid: Prenatal Stress Predicts Increased Psychiatric Morbidity during Late Adolescence and Early Adulthood in Soweto, South Africa

Abstract

Background: South Africa's rates of psychiatric morbidity are among the highest in sub-Saharan Africa and are foregrounded by the country's long history of poverty, repression and political violence during *Apartheid*. Recent evidence for prenatal influences on adolescent mental health suggests that maternal trauma exposure during gestation may intergenerationally impact the developing fetus and affect the future child's risk for psychiatric morbidity. We aimed to evaluate the intergenerational effects of prenatal stress and trauma experienced during *Apartheid* on psychiatric morbidity measured at 17-18 years of age and also evaluated the potential ameliorative effects of prenatal social support.

Methods: Participants (n = 1051) come from Birth to Twenty Plus, a longitudinal birth cohort study in Soweto-Johannesburg, South Africa's largest peri-urban township which was the epicenter of violent repression and resistance during the final years of the *Apartheid* regime (1990-1994). Pregnant women were prospectively enrolled in 1990 and completed questionnaires assessing traumatic events and social support, and their children's psychiatric morbidity were assessed at age 17-18.

Results: Full data were available from 304 mother-child pairs in 2007-8. Pregnant women who experienced worse traumatic stress in 1990 had children who exhibited greater psychiatric morbidity during late adolescence in 2007. This relationship was only significant, however, when we assessed the interactions between prenatal stress and three separate moderators. Younger maternal age and greater past traumatic life events interacted with higher prenatal stress scores to significantly predict elevations in psychiatric morbidity. Prenatal social support did not appear to buffer the long-term impacts of prenatal stress on future psychiatric morbidity.

Conclusion: Younger maternal age and greater past adolescent trauma interacted with greater prenatal stress to predict adverse psychiatric outcomes during late adolescence and young adulthood. Our findings suggest that prenatal stress may affect adolescent mental health, have stress-sensitizing effects, and represent possible intergenerational effects of trauma experienced under *Apartheid* in this sample of South African mothers and children in Soweto-Johannesburg.

5.1 Introduction

South Africa's rates of mental, neurological, and substance use disorders are among the highest in sub-Saharan Africa. In 2016, the estimated 12-month prevalence for any psychiatric disorder was 16.2%, or approximately 9.1 million individuals (GBDCN 2017). Despite these elevated rates of psychiatric morbidity, access to mental health treatment is poor: only 27% of patients living with severe mental illness are expected to receive treatment (Herman et al. 2009). The current state of public mental health in South Africa is foregrounded by a long and recent history of institutionalized White supremacist policies implemented during the *Apartheid* regime (c. 1948-1994). This period was characterized by systematic disenfranchisement of non-White communities through various modes of social, economic, and political oppression (Beinhart 2001). Despite the legislative end of *Apartheid* policies and the birth of a new democratic in 1994, South African society continues to be plagued by the persistent societal institutions of *Apartheid*, including chronic poverty (Gibbs et al. 2018), discrimination (Kuzawa & Sweet 2009), and racialized class inequality (Adjaye-Gbewonyo et al. 2016; Burns 2015), all of which are known risk factors for psychiatric disorders (Allen et al. 2014; Moomal et a. 2009; Myer et al. 2008).

In addition to these ongoing societal effects of poverty, structural violence and inequality, there is growing evidence, from South African studies and other populations, that the stressors of the past could have lingering biological effects that continue to influence socio-emotional behavior and mental health across the lifecourse. Growing evidence from the fetal origins of health and disease framework shows that past stress and trauma exposures, particularly those that occur during early development, can durably alter the development and function of various stress

regulatory mechanisms in humans, including the immune system, cardiovascular system, neurobiological function, and neuroendocrine pathways (Barker et al. 1999; Gluckman & Hanson 2004; Kuzawa 2008; Taylor et al. 2010; Heim et al. 2019). Recent findings also suggest that these stress-linked alterations in stress physiology may also affect the developing offspring through various pathways of genetic and non-genetic inheritance. For instance, large population-based studies in the United Kingdom show that greater levels of maternal prenatal stress are associated with an increased future risk for externalizing disorders in their children, such as attention deficit hyperactivity disorder (Rice et al. 2010), conduct disorders (MacKinnon et al. 2018), and internalizing disorders like anxiety and depression among adolescents (O'Donnell et al. 2014; Sharp et al. 2015). Additionally, the intergenerational signatures of maternal prenatal stress exposure have been reported in offspring during adulthood in large cohort studies and across various contexts such as Australia, the Philippines, and the United States (Betts et al. 2015; DeSantis et al. 2015; Entringer et al. 2009).

While the specific biological mechanisms that underlie the long-term psychiatric effects of prenatal stress are unknown, growing evidence from the literature on the fetal origins of psychopathology suggests that prenatal stress exposure alters the development, function, sensitivity of human stress physiological systems across the life course, which in turn may elevate one's risk for a psychopathological presentation. These stress-sensitive systems include the immune system, the catecholamine-producing sympathetic-adrenal-medullary (SAM) axis, and the hypothalamic-pituitary-adrenal (HPA) axis, which regulates physiological reactions to stress through stress-sensitive hormones like cortisol. Maternal stress-induced elevations in cortisol can enter maternal circulation, penetrate the placental wall, and reach the gestational

environment of future offspring, thereby impacting the development of fetal stress physiology (D'Anna-Hernandez et al. 2012; O'Donnell et al. 2009).

Greater fetal exposure to cortisol is understood influence a wide variety of biological and health phenotypes across the lifecourse. These include birth outcomes such as restricted fetal growth rates, shorten gestations, and reduce birth size (Kim et al. 2020a; Rosa et al. 2019; Ryu 2019). Greater intrauterine cortisol exposure may also durably alter the development and sensitivity of the fetal stress physiology (e.g. HPA axis, immune system, brain development), which together with the maternal and placental systems, may have sustained impacts on the child's stress physiology across their lifecourse (Brand et al. 2010; DeSantis et al. 2015; Entringer et al. 2009; Karlén et al. 2013). Early life stress-linked dysregulation of stress physiological mechanisms, characterized by altered diurnal cortisol rhythms, glucocorticoid resistance, chronic low-grade inflammation, and modulated brain function, has consistently been reported as both a prospective risk factor and cross-sectional neuropsychiatric phenotype of a range of psychiatric illnesses, including depression, psychosis, suicidal ideation, schizophrenia, across the lifespan (Doane et al. 2013; Heim et al. 2019; Jarcho et al. 2013; Miller et al. 2011; Taylor 2010; Vrshek-Schallhorn et al. 2013).

Additionally, recent evidence has also suggested that alterations in stress physiological systems (e.g. neuroendocrine, inflammatory, molecular, and structural pathways) due to developmental stress exposure may also alter sensitization to future stressors. The stress sensitization hypothesis (Hammen et al. 2000) proposes that the risk for adult mental illness following stressful life events is higher among individuals with a history of developmental trauma than among individuals without a history of developmental trauma. Recent findings have extended this hypothesis to suggest that greater early life trauma sensitizes or potentiates future

reactions to stress and consequently, increases psychiatric disease risk (Heim et al. 2019; McLaughlin et al. 2010; Shapero et al. 2014). While an increasing number of studies are noting the long-term impacts of prenatal stress on infant, child, and early/mid adolescent psychological status (Ilg et al. 2019; Koss & Gunnar 2018; Ping et al. 2020; Ziljmans et al. 2015), few studies have examined the mental health impacts of prenatal stress into late adolescence and adulthood and also evaluated the potential stress sensitization effects of prenatal stress (Koss & Gunnar 2018; Ping et al. 2020; Ziljmans et al. 2015).

This emerging evidence suggests that some proportion of the mental health burden of current populations could reflect the lingering biological imprint of past traumatic experience during gestation (Barker 1999; Krontira et al. 2020; Kuzawa & Sweet 2009). South Africa's recent history and the country's tumultuous transition into democracy raise the question of whether the traumas of *Apartheid* may continue to have lasting effects, influencing risk for psychiatric morbidity across generations (Kim 2020). It furthermore raises the question of whether some of these effects might be reversible, opening opportunities for public health interventions to reduce the societal burden of psychiatric morbidity (Heim et al. 2019). However, little work in South Africa has explored this hypothesis and its contribution to mental health. Furthermore, as the most current research is conducted in high-income, Western contexts, it remains unclear if these effects are seen in non-Western, low- and middle-income contexts like South Africa, where adverse psychosocial and environmental conditions are more prevalent and where the burden of mental illness is substantially greater (Patel 2007; Vigo et al. 2016).

This study examines the long-term impacts of prenatal stress and trauma from South African *Apartheid* on psychiatric morbidity during late adolescence/early adulthood and the possible reversibility of the long-term effects of prenatal stress in a longitudinal birth cohort

study. Adolescence is an important period in the development of future mental illness as most psychiatric conditions emerge during this stage (Patel 2007; Breslau et al. 2017) and because adolescent psychiatric disease is a major risk factor for future adult mental illness (Pine et al. 1993; Sawyer et al. 2012). The recent history of *Apartheid*, high rates of mental illness, and low rates of healthcare access emphasize the need to elucidate possible mechanisms underlying the intergenerational mental health effects of prenatal trauma in order to improve public mental health in South Africa.

5.2 Methods

Study setting and participants

Data come from a longitudinal birth cohort in South Africa called Birth to Twenty Plus (Bt20++), which currently spans three generations of families in the greater Johannesburg-Soweto area. The Birth to Twenty (Bt20++) study is both the largest and longest running longitudinal birth cohort study of child health and development in Africa. Bt20++ emerged as a collaboration between the University of the Witwatersrand in Johannesburg and the South African Medical Research Council with the aim to assess the impacts of rapid urbanization towards the end of *Apartheid* on the growth, health, well-being, and educational progress of children. Soweto is the largest township outside of the city of Johannesburg and a site of immense cultural and historical significance in the struggle against *Apartheid*. Racial and political violence, government divestment, and widespread protest were common in both cities, particularly at the legislative end of *Apartheid*, which is when pregnant women were first recruited into the study.

All singleton live births delivered in public sector hospitals between April 23 to June 8, 1990 and who were residents in the metropolitan Johannesburg-Soweto area six months after delivery were enrolled in Bt20+ (Richter et al. 2007). In late 1989, BT20+ began interviewing pregnant women in public antenatal clinics to identify potential participants whose births would fall within the enrollment period. Enrolled Bt20+ neonates were cross-checked with all government birth notifications during the 7-week time period. The study area covered approximately 78 square miles at the time and included close to 3.5 million people, with about 400,000 informal housing units.

A total of 3273 singleton children were enrolled in Bt20+ and 72% of the initial cohort continued to participate in the study after 17 years (Norris et al. 2007). The cohort is roughly representative of the demographic parameters of the metropolitan Johannesburg-Soweto region. Currently, the cohort underrepresents White children due to cohort enrollment taking place in public health facilities; White families were more likely to utilize private practitioners and facilities Although BT20+ children were all *in utero* during the *Apartheid* regime, they became among the first generation born into a democratic South Africa, and colloquially known as "Mandela's Children" because they were born shortly after Nelson Mandela's release from prison on February 11, 1990. Between 1990 and 2007, the scope of this analysis, BT20+ families participated in 18 waves of data collection, and follow-up studies continue. All participants provided assent and their parents provided written, informed consent. Ethical approval was obtained from the University of Witwatersrand Committee for Research on Human Subjects.

Before the full sample was achieved, 1594 women were interviewed during their third trimester about their pregnancy, social experience, and household conditions. Antenatal interviews were conducted by seven trained, multilingual, interviewers. Where translation of

measures was required, consensual agreement on the phrasing of questions was reached. Continuous translation and back- translation were used in order to ensure that the meaning/s attained in the destination language mirrored those intended in the original one. The majority of interviews were conducted in antenatal services, with a quarter conducted at home. Zulu, Sotho and English were the most common languages used. Adolescents were interviewed in a research facility at the Chris Hani-Baragwanath Hospital in Soweto and at home.

Prenatal stress and social support

Prenatal stress exposure (G1) during the third trimester of pregnancy was collected using a 16-item scale ($\alpha = 0.64$), adapted from Bluen et al. (1988) capturing information on exposure to various forms of family and community stresses, including police violence, injury, and incarceration. Yes/no responses indicated the presence or absence of each stressor during the previous 6 months. After exploratory analyses, two questions were dropped: one due to a low response rate (have you experienced any problems with your other children?) and the other due to contradictory concepts being assessed at once (domestic and familial violence vs. partner separation). Of the initial 1594 women, 1051 women (65.9%) completed all of the remaining prenatal stress questions.

Social support was measured using a series of four, yes/no questions to identify the absence or presence of instrumental and emotional support, including: people available to help, a confidante, being able to speak to her partner, belonging to a community organisation/church. All questions were summed to create a total score.

Demographic, Health, and Socioeconomic Variables

During the antenatal visit in 1990, expectant women were asked about their current housing situation (e.g. number of rooms, number of inhabitants), population group (i.e. "race"), marital status, age, and obstetric history. Gravidity was calculated from information on obstetric history and operationalized into a categorical yes/no variable (0 = no past pregnancy, 1 = past history of pregnancy). They were also asked whether they used tobacco or had been drinking alcohol during their pregnancy. At delivery, a series of questions about the neonate were administered to gather information about gender, birth order, birthweight, and gestational age. Birthweight (g) and gestational age (weeks) were obtained from the child's Road to Health Card, a patient-held child medical record provided to all new mothers in South Africa.

Household socio-economic status (SES) was assessed using an asset index which scored each participant according to the number of household physical assets that they possessed out of a possible 6 (e.g. television, refrigerator, washing machine, radio, telephone, home ownership, car). Household SES was measured again in 2006 using an updated list of assets (e.g. television, car, washing machine, refrigerator, phone, radio, microwave, cell phone, DVD, MNET, DSTV, computer, and internet). The asset index was designed based on standard measures used by the Demographic and Health Surveys (https://dhsprogram.com/), based on the work of Filmer and Pritchett (1999). To capture the overall SES environment during prenatal development and 2007, when the outcome measure was administered, an aggregate SES variable was constructed by summing standardized assets scores from both years of data collection.

Household Stressful Life Events

The occurrence of stressful life events in the household were assessed across two timescales, six months and twelve months, and reported by the caregiver of the index child based on yes/no responses.

Thirteen life events were assessed and summed together to create a composite measure of household stress that occurred during the past six months, which included death of a sibling, parent, and other family member (three separate questions), divorce, index child changing schools, a serious illness or hospitalization experienced by the index child, caregiver, and family member (three separate questions), marital separation, increase in arguments with partner, caregiver separation from family for two weeks or more, a child leaving home, and unemployment. Additionally, eight life events that occurred in the last year were summed to create a separate composite measure, which assessed whether any member of the household experienced robbery, harassment, threats, sexual molestation, physical violence, and murder.

General Health Questionnaire (GHQ-28)

The General Health Questionnaire (GHQ-28) is a psychological screener that provides a measure of psychiatric morbidity based on four 7-item scales: somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression (Goldberg & Hillier 1979). It assesses changes in mood, feelings, and behaviours during the past four weeks. The respondent evaluates their occurrence on a 4-point Likert scale, "less than usual," "no more than usual," "rather more than usual," and "much more than usual." Seven questions are reverse scored and transformed before all responses summed. Bt20+ index children and their caregivers completed the GHQ during a follow-up wave of data collection when the index children were 17-18 years old.

Statistical analyses

All analyses were conducted using version 15.1 of Stata (Stata Corporation, College Station, TX). All variables were examined for normal distribution and outliers. Bivariate analyses were conducted between prenatal stress, psychiatric morbidity at age 18, and covariates. Covariates were included based on a priori knowledge of social, biological, and obstetric risk factors that may potentially confound the relationship between prenatal stress and later-life psychiatric morbidity (de Mola et al. 2014; Entringer et al. 2009; O'Donnell et al. 2013). The following variables were considered for inclusion as confounding factors: maternal age, maternal education, marital status, gravidity, tobacco use, and alcohol consumption during pregnancy, household density (ratio of the number of inhabitants to the number of rooms available for sleeping), social support, and child gender. ($p > 0.10$). Fetal growth rate and gestational age were also included as key covariates to examine the role of fetal growth restriction and preterm delivery as possible pathways by which prenatal stress affects late adolescent psychiatric morbidity. A proxy measure of fetal growth was created by regressing birthweight on gestational age to create standardized residuals.

Bivariate analyses were conducted to identify potential confounding variables for inclusion in the final analytic models. With the exception of known confounding factors for the relationship between prenatal stress and later life psychiatric morbidity, only those that were statistically significant at the 0.1 level were included in the final models. These variables included infant gender, aggregate SES, gravidity, perceived social support during pregnancy, maternal education during pregnancy, household density, alcohol consumption during pregnancy, tobacco use during pregnancy, fetal growth rate, gestational age, maternal age, recent stress, past stress, and maternal GHQ in 2007. Multiple ordinary least squares (OLS) regressions

were conducted to examine the impact of prenatal stress on late adolescent psychiatric morbidity.

The final analytical sample included 304 mothers and adolescents with requisite data (Table 1). Participants included in the analytical sample were similar to those excluded (n = 747) with respect to psychiatric morbidity at 17-18 years, prenatal stress, child gender, gravidity, alcohol consumption, tobacco use, social support, household density, SES in 2008, fetal growth rate, recent stress, past stress, and maternal psychiatric morbidity ($p > 0.05$). Birthweight, gestational age, SES in 1990, maternal education in 1990, and the aggregate SES measure were significantly different from those excluded from the sample ($p < 0.05$). Children in the analytical sample exhibited higher birthweights and slightly longer gestations. Additionally, participants in the analytical sample reported lower household SES in 1990, lower aggregate SES levels, but more educated mothers in 1990. Thus, the analytic sample is somewhat disadvantaged compared to excluded group.

5.3 Results

In our sample of 304 mothers and adolescent pairs, the average number of traumatic events experienced within the past six months of the interview was 2.4/15 total events, while the average number of social support resources was 2.8/4 (Table 1). About 24% of the sample, or 74 adolescents, surpassed the cutoff (51/112) for high psychological morbidity based on their GHQ scores. Table 2 presents the results of the OLS regression analyses of fetal, maternal, behavioral, and environmental factors that predict psychiatric morbidity during late adolescence. The unadjusted model (Model l) predicting GHQ scores on prenatal stress was positive although not significant ($\beta = 0.53$, $p = 0.169$). The effect of prenatal stress did not substantively change after

adjusting for gender or maternal age (Model 2). We tested for an interaction between prenatal stress and gender, but we found no evidence for gender differences. The relationship between prenatal stress and psychiatric morbidity strengthened and approached significance (β = 0.69, p = 0.066) after including gestational variables, specifically gravidity, gestational age, and fetal growth (birthweight adjusted for gestational age) (Model 3). Greater fetal growth rates significantly predicted greater adolescent GHQ scores (β = 0.035, p = 0.037). Adjusting for maternal pregnancy exposures (Model 4), stress measures and maternal GHQ (Model 5), socioeconomic markers (Model 6), and prenatal social support (Model 7) did not appreciably modify the relationship between prenatal stress and adolescent GHQ, but the effect of prenatal stress falls out of significance in Model 6.

Testing moderators of prenatal stress-later life psychiatric morbidity pathway

We next assessed factors that could moderate the relationship between PNS and future psychiatric morbidity in the index generation: maternal age, recent/past stress, and social support. We examined the effect of an interaction between gender and prenatal stress on psychiatric morbidity, and results showed a non-significant interaction between prenatal stress and male (β = -0.46, F[1, 287] = 0.35, p = 0.556). Model 8 reports a negative and significant interaction between maternal age and prenatal stress severity (β = -0.17, F[1, 287] = 7.14, p = 0.008), showing that the adverse psychiatric effects of prenatal stress are stronger in children with younger mothers (Figure 2).

To assess the stress-sensitization hypothesis, we evaluated the interaction between prenatal stress and both measures of household stress from the past six and twelve months. Our results reported a non-significant interaction between prenatal stress and recent household stress

from the past six months (β = -0.027, F[1, 287] = 0.001, p = 0.951) and a significant interaction between prenatal stress and past household stress from the past year (Model 9: β = 1.19, F[1, 287] = 4.52, p = 0.0343) Figure 3). The effect of prenatal stress on late adolescent and early adult psychiatric morbidity was stronger in index children living in households with greater stress and trauma exposure. Finally, to explore the possible effects of positive maternal social environments during pregnancy in ameliorating the long-term mental health impacts of prenatal stress, we evaluated the effect of an interaction between social support and prenatal stress on psychiatric morbidity. Results reported a non-significant interaction between social support and prenatal stress (β = -0.092, F[1, 287] = 0.04, p = 0.836).

5.4 Discussion

In this longitudinal study of the intergenerational mental health impacts of prenatal stress in South Africa, we find that pregnant women who reported greater trauma exposure during *Apartheid* had children who exhibited greater psychiatric morbidity during late adolescence, 17-18 years after the timing of their fetal stress exposure. This relationship, however, was only significant after interacting greater prenatal stress with younger maternal age (p = 0.008) and greater household stress and trauma in the past year (p = 0.0343) and remained statistically significant after controlling for key demographic, social, and biological characteristics. In sum, these data shed light on the potential fetal origins of late adolescent mental health and the intergenerational effects of trauma from *Apartheid* in our birth cohort sample of South African mothers and children in Soweto-Johannesburg. This study is among the first to prospectively assess the long-term psychiatric impacts of prenatal stress into early adulthood in a low- and middle-income country.

The finding that greater prenatal stress predicts future psychiatric morbidity is consistent with the growing literature on the fetal origins of later life psychopathology (Abbott et al. 2018; Bosch et al. 2012; Davis et al. 2020; O'Donnell et al. 2013; Ping et al. 2020). Retrospective and prospective studies of prenatal stress show that greater maternal social adversity during pregnancy predicts elevated risks for developing psychopathologies like depression, psychosis, and schizophrenia in the future (Lipner et al. 2019; McQuaid et al. 2019; Van den Bergh et al. 2008). The long-term, intergenerational effects of prenatal stress, however, were only significant when the moderating effects of maternal age and past traumatic life events on prenatal stress were independently assessed.

Our findings on the interaction between prenatal stress and younger maternal age corroborate past research highlights the numerous socioeconomic, gendered, and cultural adversities faced by younger pregnant mothers and their families in Soweto and other communities in South Africa (Makola 2011; McLeod 1999; Richter et al. 2006; Willan 2013). Young motherhood in Soweto is understood to be a highly stigmatized and morally compromised status in Soweto and a period of greater vulnerability to certain forms of violence in Soweto and other communities in South Africa (Panday et al. 2009). Past research in Bt20+, Soweto, and elsewhere shows that young mothers frequently receive disappointment and negative attitudes from their parents, ridicule and shame from nurses, and stigma from community members (Makola 2011; McLeod 1999; Richter et al. 2006; Willan 2013) and that infants of young teenage mothers were lighter at birth relative to neonates from older mothers (Cameron et al. 1996; Lundeen et al. 2016; Rothberg et al. 1991). Our data also showed that both younger age was associated with lower birthweight. The long-term developmental effects of lower birthweight are well-documented – lower birthweight is associated with increased risk for

a wide range of adolescent and adult mental illness risk across the lifecourse (Abel et al. 2010; Barker 2004; Lærum et al. 2019; Orri et al. 2019).

Results also show that fetal growth, but not gestational age, is an important predictor of later life psychiatric morbidity in this sample. Fetal growth was positively and significantly related to late adolescent/early adulthood psychiatric morbidity. Also, our finding that fetal growth weakens the coefficient on prenatal stress after inclusion into the model provides preliminary evidence that fetal growth may be involved in the relationship between prenatal stress and adolescent psychiatric morbidity. The direct effect of fetal growth rate on psychiatric morbidity at 18, however, conflicts with past literature on the fetal origins hypothesis that suggests that adverse intrauterine exposures and slower fetal growth, potentially due to stress-induced alterations in gestational neuroendocrine activity, can durably impact health, development, and disease risk in the next generation (Kuzawa 2008; O'Donell & Meaney 2017; Monk et al. 2019). Past studies have shown sex differences in fetal growth rates and preterm birth with boys typically showing higher incidence of adverse birth outcomes (Di Renzo et al. 2007), yet there were no significant sex differences in fetal growth rates, gestational age, nor birthweights in this sample. Further research in Bt20+ should examine the potential sex differences in fetal growth rates due to prenatal stress.

Our data show that recent stress from the past 6 months was a positive and marginally significant predictor of psychiatric morbidity at 17-18, while the effect of traumatic life experiences from the past 12 months was only significant when interacted with prenatal stress. The significant interaction between prenatal stress and past year traumatic experiences, showing that the direct relationship between prenatal stress and psychiatric morbidity is stronger in children with greater household traumatic events, provide supporting evidence for the stress

sensitization hypothesis (Hammen et al. 2000; McLaughlin et al. 2010; Van den Bergh et al. 2008). While the data show that prenatal stress itself may not have sensitizing effects on later life psychiatric morbidity, it is only after interacting with elevated levels of past stress that the long-term sensitizing effects of prenatal stress on later life psychiatric morbidity become apparent. The stress sensitizing effect of prenatal stress may only significantly interact with past stress (from the past 12 months) trauma rather than with recent stress (from the past six months) because of the nature of the experiences queried by each measure. Reported by the mother during the interview, our composite measure of past stress consisted of eight questions assessing a collection of objective traumatic events that are more likely to have household-level impacts specifically on the index child compared to the events assessed in the recent stress variable. Also reported by the mother, our measure of recent stress may also query household experiences that may have marginal to no impact on the index child's psychiatric morbidity. These experiences include unemployment, divorce, or death of a relative. Nevertheless, our data show interesting stress sensitization effects due to the interaction between prenatal stress and household stress exposure from the past year.

Given these data and existing findings on the fetal origins of late adolescent/early adult psychopathology, there are two possible developmental mechanisms that may facilitate the lasting impacts of prenatal stress on future psychiatric morbidity. First, increased severity of prenatal stress may cause durable increases in psychological and physiological stress reactivity (e.g. HPA axis, the immune system, and brain function) into adulthood, which may make individuals respond worse to future stressors, and in turn increase one's risk of developing a psychopathology (Hammen et al. 2000; Heim et al. 2019; Kendler et al. 2004; McLaughlin et al. 2010). In one study, researchers found that women who experienced greater maternal anxiety

during pregnancy were more likely to have children with flattened diurnal cortisol slopes, which predicted depression in female adolescents (Van den Bergh et al. 2008). The growing literature on the long-term health effects of prenatal stress is consistent with the larger body of scholarship on the effects of postnatal early life stress, which are known to have similar lasting effects on neuroendocrine, inflammatory, and molecular mechanisms across development, extending into adulthood (Gustafsson et al. 2010; Heim & Binder 2012; Taylor et al. 2010).

Second, greater histories of prenatal stress may increase the severity of behavioral and psychiatric conditions that increase emotional and biological sensitization to future stressors and adverse events, such as depression, anxiety, and other mood disorders. Additionally, the major symptoms of depression, such as persistent feelings of victimization, learned hopelessness and helplessness, and negative appraisal (Folkman & Lazarus 1986; Peterson & Seligman 1983) may have elevated individual sensitivity to and appraisal of recent stressful events (Medrano & Hatch 2005; Peterson & Seligman 1983) and neuroendocrine sensitization (Stroud et al. 2011) to future stressors. Thus, greater sensitivity to and appraisal of past stress may have emerged as a function of the long-term depressive and psychological effects of prenatal stress. Future longitudinal research is needed to determine the underlying stress physiological mechanisms by which prenatal stress influences future stress sensitivity and psychopathological morbidity.

Additional stress physiological mechanisms and external social processes may also explain the late adolescent psychiatric impacts of prenatal stress in our sample. Growing research report that higher levels maternal prenatal stress corresponds with greater pro-inflammatory cytokines levels and other inflammatory markers across adulthood (Bilbo & Schwarz 2009; Entringer et al. 2008; Plant et al. 2016; Slopen et al. 2015). Scientists have also found increasing evidence that greater maternal prenatal stress and social experience predicts epigenetic changes

at genetic loci affecting neuroendocrine systems, neurotransmission, and neurogenesis in their children (Barker et al. 2018; Glover et al. 2018; Ostlund et al. 2016; Provenzi et al. 2020). While we cannot completely rule out the potential role of certain stress physiological mechanisms in driving the prenatal stress-late adolescence relationship without directly assessing the system (e.g. salivary cortisol, cytokines, etc.), multiple stress-sensitive biological pathways likely contribute to elevations in psychiatric risk at the same time. Finally, prenatal stress may be indicative of larger and longer-term socioeconomic patterns of mothers and children in Soweto. Substantial evidence illustrates the durable impacts of poverty and material deprivation during pregnancy. Chronically low socioeconomic status between gestation and adulthood predicted flatter diurnal cortisol rhythms in a large sample of Filipino adults (DeSantis et al. 2015).

We also report that perceived social support during pregnancy did not buffer against the later-life effects of trauma exposure during pregnancy. Prenatal social support did not appear to have an independent protective effect on adolescent psychiatric morbidity, yet the presence of a partner during pregnancy did significant predict lower adolescent GHQ scores. The insignificant effect of prenatal social support on future psychiatric morbidity, either from a direct protective effect on adolescent mental health or buffering against the psychiatric impacts of prenatal stress, may be attributed to the limited strength of our social support measure, which primarily assessed interpersonal support and a single, dichotomous measure of group membership.

Psychologists have emphasized the importance of assessing the degree, frequency, and timing, and modes of social support, similar to the impacts of stress and trauma, when examining psychosocial and physiological impacts (Dunkel Schetter 2011; Orr 2004) Past studies report protective effects of prenatal social support on postnatal outcomes, including better infant birth outcomes (Feldman et al. 2000; Orr 2004) and lower child adiposity (Katzom et al. 2019).

Prenatal social support, in the form of a presence of a partner during pregnancy, has also shown to buffer the adverse effects of prenatal social adversity to predict better cognitive and psychiatric outcomes in children (Spann et al. 2020). Finally, early evidence suggest that prenatal social support may buffer against the impacts of maternal stress and contribute to healthier cortisol regulation (Field et al. 2013; Luecken et al. 2013). Further research is necessary to identify both the protective and buffering effects of prenatal stress to ameliorate the long-term disease outcomes of intergenerational stress and trauma.

In many past published studies of the lifecourse impacts of adverse prenatal experience, the source of maternal social adversity stem from violent and oppressive conditions linked with political turmoil, war, famine, and numerous forms of social inequality (Yehuda et al. 2016; Kertes et al. 2016; Roseboom et al. 2006; Kim et al. 2020). Despite the formal end to these forms of political violence, the developmental and health consequences of trauma exposures among pregnant women can durably extend across the lifecourse of the future child and may even impact the subsequent generation (Barbarin & Richter 2013; Kuzawa & Sweet 2009). These developmental pathways and health consequences of embodied trauma may represent mechanisms that drive mental health inequalities that disproportionately impact marginalized populations with high levels of stress and trauma exposure. Inasmuch as scientists aim to reverse the past impacts of embodied trauma and social oppression, the ongoing legacies of these violent histories and historical traumas, such as *Apartheid*, must be recognized and addressed to prevent future mental health inequities from emerging.

Limitations

Unfortunately, the timeframe of the queried stress exposure in the prenatal stress measurement does not specify the exact moment of exposure as the participants were asked to report stressors that occurred in the past six months. Women completed the antenatal stress questionnaire during their third trimester, meaning that the reported stressor could have occurred anytime between the first and third trimester. Future research will benefit from knowing the exact periods of prenatal stress and cortisol exposure to understand the potential developmental and physiological effects on the child.

5.5 Conclusion

In this analysis of the intergenerational mental health impacts of prenatal stress in a large birth cohort in Soweto, South Africa, our data show that pregnant women who reported greater trauma exposure during *Apartheid* had children who exhibited greater psychiatric morbidity during late adolescence and early adulthood, 17-18 years after the timing of their fetal stress exposure. This relationship, however, was only significant among children born to younger mothers and children exposed to household adversity in the past year. These findings suggest that greater prenatal stress may adversely affect adolescent mental health, have stress-sensitizing effects in children, and represent possible intergenerational effects of trauma experienced under *Apartheid* in this sample of South African mothers and children in Soweto-Johannesburg.

5.6 Tables & Figures

Figure 1. Map of Johannesburg and Soweto

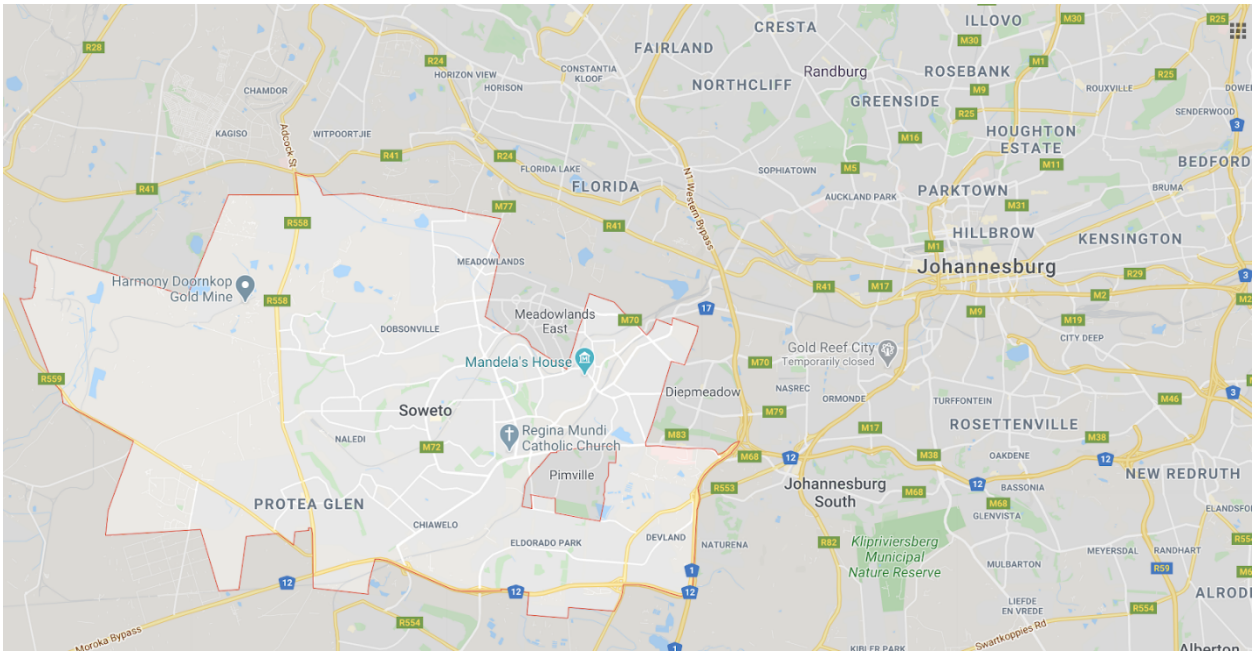
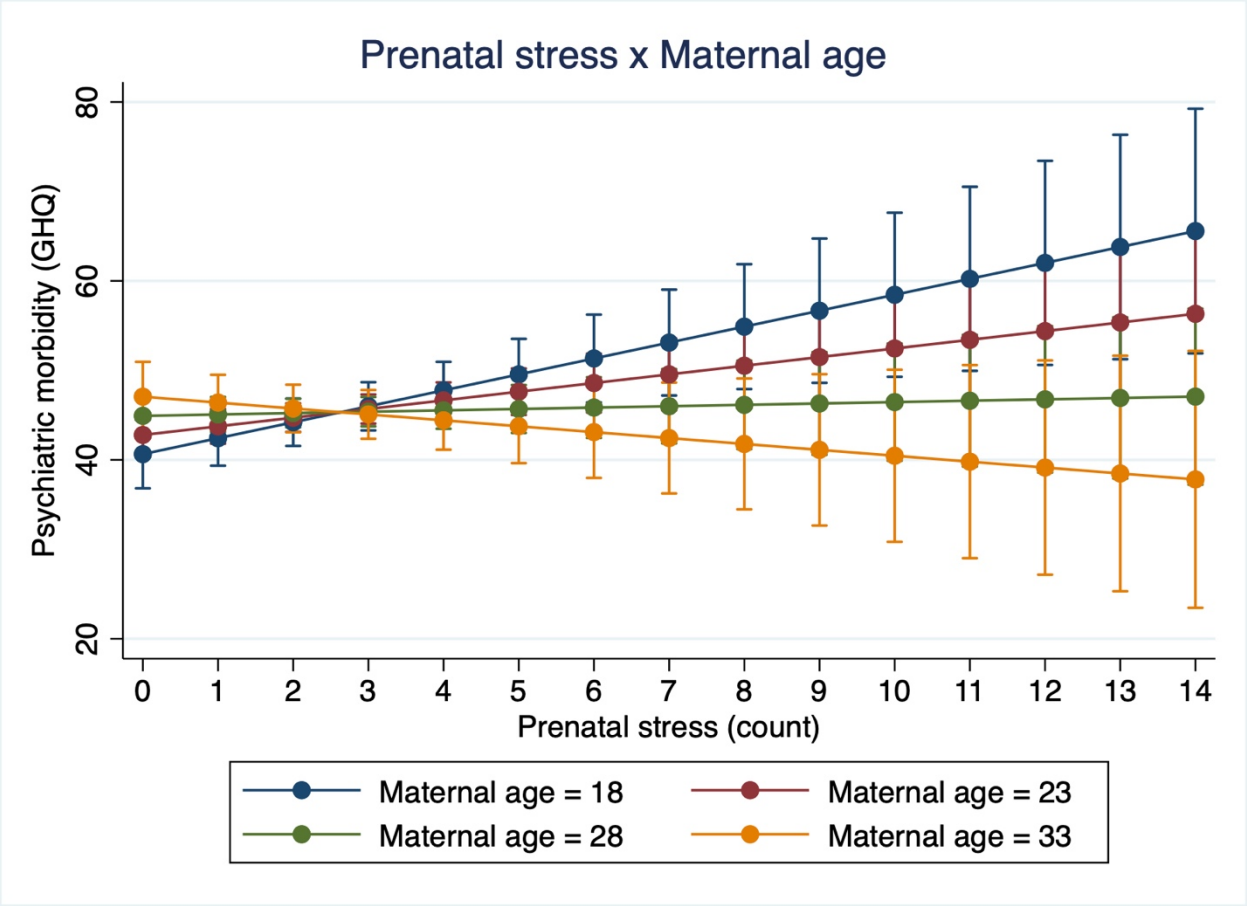
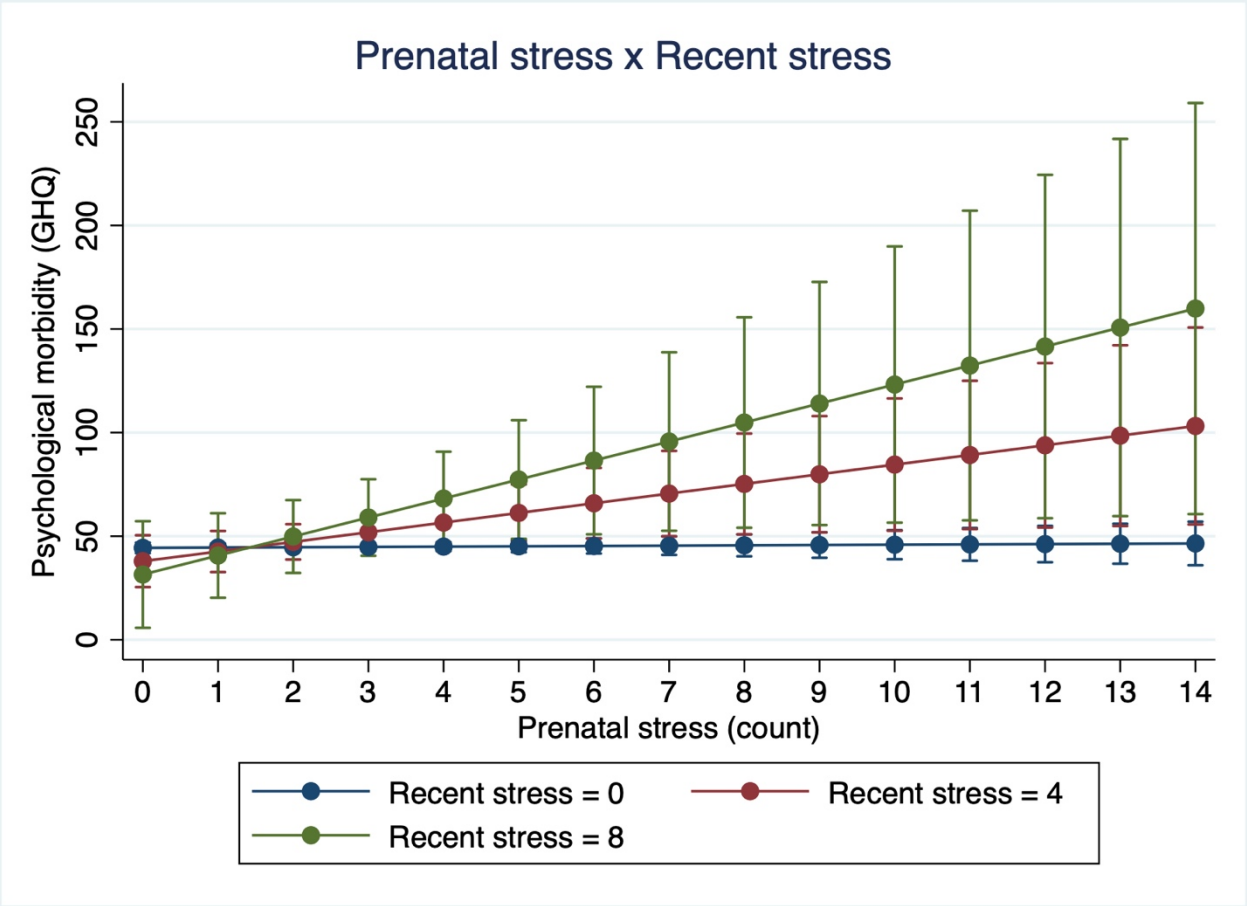


Figure 2. Interaction effect between prenatal stress and maternal age predicting psychiatric risk.



Note. This figure demonstrates the interaction effect between prenatal stress and maternal age predicting adolescent psychiatric risk at Year 17. The effect of prenatal stress on late adolescent psychiatric risk is much stronger among younger mothers (β = -0.17, F[1, 287] = 7.14, p = 0.008). There were significant main effects for prenatal stress and maternal age.

Figure 3. Interaction effect between prenatal stress and household stress and trauma in the past year predicting psychiatric risk.



Note. This figure demonstrates the interaction effect between prenatal stress and recent stress predicting adolescent psychiatric risk at Year 17. The effect of prenatal stress on late adolescent psychiatric risk is stronger as the degree of recent stress increases ($\beta = 1.19$, $F[1, 287] = 4.52$, $p = 0.0343$). There were no significant main effects for prenatal stress and recent stress.

5.6 Tables and Figures

Table 1. Demographic characteristics, prenatal conditions, and psychiatric morbidity

Variables	N = 304	Mean (SD)	%	Range
Demographics				
Gender (% male)	143		47.04	
Population Group ("Race")				
Black	270		88.8	
Coloured	31		10.2	
Indian	3		1.0	
Maternal age (at enrollment)		25.5 (6.0)		15 – 43
Maternal educational attainment (% attended)				
No school or primary school	33		10.9	
Secondary school	244		79.7	
Professional/teaching/university	27		8.9	
Household density (people/room)		3.5 (1.7)		0.67 – 16
Household assets at 1990		3.9 (1.7)		0 – 7
Household assets at 2006		6.6 (2.4)		1 – 13
Maternal alcohol use in 1990				
Never	285		93.8	
Few times a year	11		3.8	
Once a month or more	8		2.6	
Maternal tobacco use in 1990				
Not at all	268		88.2	
Occasionally	13		4.3	
Daily	23		7.5	
Marital status				
Married/Partnered	90		29.6	
Single/Widowed	214		70.4	
Birthweight (g)		3149.2 (443.8)		1150 – 4550
Low birthweight (<2500g)	20	2262.3 (292.8)	6.6	1150 – 2485
Gestational age (weeks)		38.3 (1.2)		32 – 43
Preterm birth (<37 weeks)	17	35.5 (1.3)	5.6	32 – 36
Psychological status				
Maternal traumatic events in 1990		2.4 (1.9)		0 – 9
Maternal Social Support in 1990		2.8 (0.9)		0 – 4
Adolescent General Health		45.2 (12.7)		28 – 96
Questionnaire (score)	74	63.3 (11.9)		52 – 96
High psychological risk (≥51)				
Social Support		2.8 (0.9)		0 – 4
Maternal General Health Questionnaire in 2007 (score)		47.5 (13.2)		28-112

Table 2. Multiple regression models of prenatal stress predicting adolescent psychiatric morbidity with covariates

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Prenatal stress (count)	0.5 ± 0.4	0.6 ± 0.4	0.7 ± 0.4†	0.7 ± 0.4†	0.7 ± 0.4†	0.6 ± 0.4	0.6 ± 0.4
Gender (male)		-5.9 ± 1.4***	-6.0 ± 1.4***	-6.0 ± 1.4***	-5.9 ± 1.5***	-5.9 ± 1.5***	-5.8 ± 1.5***
Maternal age (year)		-0.1 ± 0.1	-0.01 ± 0.1	-0.02 ± 0.1	0.03 ± 0.2	0.02 ± 0.2	0.04 ± 0.2
Gravidity (yes/no)			-3.1 ± 1.8†	-3.1 ± 1.8†	-3.3 ± 1.9†	-3.9 ± 1.9*	-3.7 ± 1.9†
Fetal growth[a]			0.004 ± 0.002*	0.003 ± 0.002*	0.003 ± 0.002†	0.003 ± 0.002†	0.003 ± 0.002†
Gestational age (week)			-0.1 ± 0.6	-0.1 ± 0.6	-0.1 ± 0.6	-0.2 ± 0.6	-0.2 ± 0.6
Alcohol (frequency)				0.01 ± 0.9	0.04 ± 0.9	0.002 ± 0.9	-0.09 ± 0.9
Tobacco (frequency)				0.7 ± 1.3	0.7 ± 1.3	0.3 ± 1.4	0.1 ± 1.4
Crowding (ratio)					-0.3 ± 0.4	-0.4 ± 0.4	-0.4 ± 0.4
Recent Stress (count)					1.4 ± 0.8†	1.5 ± 0.8†	1.5 ± 0.8†
Past Stress (count)					1.0 ± 1.2	1.1 ± 1.2	1.0 ± 1.2
Maternal GHQ (score)					-0.02 ± 0.06	-0.03 ± 0.06	-0.04 ± 0.06
Assets (count)						-0.3 ± 0.5	-0.2 ± 0.5
Maternal education (count)						-0.9 ± 0.9	-0.8 ± 0.9
Social support (count)							-0.9 ± 0.9
Intercept	43.9 ± 1.2***	50.2 ± 3.3***	54.0 ± 22.4*	52.1 ± 22.8*	53.8 ± 23.3*	59.4 ± 24.2*	62.9 ± 24.4*
Model R^2	0.0063	0.0641	0.0858	0.0866	0.0986	0.1037	0.1071

†p <0.1 *p < 0.05 **p < 0.01 ***p < 0.001

[a] Birthweight adjusted for gestational age

	Model 8	Model 9
Prenatal stress (count)	4.8 ± 1.6**	0.1 ± 0.5
Prenatal stress x Maternal age	-0.2 ± 0.1**	
Prenatal stress x Past Stress		1.2 ± 0.6*
Gender (male)	-5.7 ± 1.4***	-5.7 ± 1.5***
Maternal age (year)	0.4 ± 0.2*	0.7 ± 0.2
Gravidity (yes/no)	-3.6 ± 1.9†	-3.8 ± 1.9†
Fetal growth[a]	0.003 ± 0.002*	0.003 ± 0.002†
Gestational age (week)	-0.1 ± 0.6	-0.2 ± 0.6
Alcohol (frequency)	-0.004 ± 0.9	-3.8 ± 1.9
Tobacco (frequency)	0.1 ± 1.4	-0.1 ± 1.4
Crowding[b] (ratio)	-0.3 ± 0.4	-0.3 ± 0.4
Recent Stress (count)	1.5 ± 0.8†	1.5 ± 0.8†
Past Stress (count)	0.9 ± 1.2	-1.6 ± 1.7
Maternal GHQ (score)	-0.03 ± 0.1	-0.04 ± 0.06
Assets (count)	-0.3 ± 0.5	-0.1 ± 0.5
Maternal education (count)	-0.7 ± 0.9	-0.7 ± 0.9
Social support (count)	-1.1 ± 0.9	-0.9 ± 0.9
Intercept	50.9 ± 24.6*	61.7 ± 24.3*
Model R^2	0.1288	0.1210

†p <0.1 *p < 0.05 **p < 0.01 ***p < 0.001

[a] Birthweight adjusted for gestational age

[b] Number of household inhabitants/rooms used for sleeping

CHAPTER 6:
Early life exposure to domestic violence and HPA axis function independently predict adult depression in metropolitan Cebu, Philippines

6.1 Introduction

Depression accounts for a large and growing burden of disease and illness worldwide and disproportionately impacts individuals living in low- and middle-income countries (Patel 2007; Vigo et al. 2016). Physical, nutritional, and psychosocial insults are known to increase the risk of adult depression and other forms of mental and physical illnesses, particularly when individuals endure these impacts during early development (Barker et al. 1999; Chapman et al. 2004). For example, previous studies have reported that histories of childhood stress and trauma elevate one's risk of developing post-traumatic stress disorder (Brewin et al. 2000), cardiovascular disease (Dong et al. 2004), and autoimmune diseases (Dube et al. 2009) during adulthood. The durable effects of early life psychosocial stress exposure predict adult depression beyond the influence of genetic predispositions, as these patterns have also been reported in twin studies (Kendler et al., 2000; Nelson et al., 2002). Elucidating the possible underlying biological mechanisms can allow for the identification of causal pathways that sustain the lasting impacts of early life experiences on adult depression and can illuminate potential opportunities to ameliorate the long-term poor health outcomes shaped by these adverse experiences.

The hypothalamic-pituitary-adrenal (HPA) axis, a primary physiological system involved in the mammalian stress response, has been implicated as an important biological mechanism linking psychosocial and environmental exposures during early development to later mental health (Heim et al. 2012; Miller et al. 2011; Taylor et al. 2011). Early life stress exposure and adverse social conditions have consistently been reported as strong predictors of HPA axis

dysregulation as indexed by abnormal diurnal cortisol rhythms and stress reactivity (Gustafsson et al. 2010; Heim & Binder 2012; Taylor et al. 2011), although the direction of these relationships has varied. For example, individuals who experienced early life stress have exhibited both higher (Luecken & Appelhans 2006; Schalinksi et al. 2015; van der Vegt et al. 2009) and lower levels of baseline cortisol (DeSantis et al. 2015; Trickett et al. 2010; van der Vegt et al. 2009) during adulthood. Early life stress also predicted altered cortisol awakening response (Butler et al. 2017; Engert et al. 2011; Fogelman & Canli 2018; Gonzalez et al. 2009) and evening cortisol levels (Engert et al. 2011; Gustafsson et al. 2010) in adulthood in varying directions. Additionally, adults with a history of child abuse and neglect have been reported to exhibit signs of HPA axis dysregulation as evidenced by greater (Heim et al. 2000; Luecken & Appelhans 2006; Pesonen et al. 2010; Vaccarino et al. 2015) and blunted levels (Cărnuţă et al. 2015; Carpenter et al. 2007; Carpenter et al. 2011; Elzinga et al. 2008; Janusek et al. 2017; Lovallo et al. 2012) of stress reactivity in response to acute psychosocial stressors. Finally, early life stress-induced HPA axis dysregulation has also been seen in non-human primate studies. Unpredictable separations from the mother, unpredictable maternal feedings, or spontaneous maternal abusive behavior among captive rhesus macaque infants were found to predict altered diurnal cortisol rhythms characterized by lower morning levels, higher daytime levels, and flatter cortisol slopes across the day (Coplan et al. 1996; Sanchez et al. 2005; Sanchez 2006). This pattern of diurnal rhythm disruption persisted for months to even years after the initial period of adversity.

Dysregulation of circadian HPA axis rhythms has consistently been characterized as a neuroendocrinological phenotype of depression in animal and human studies (Adam et al. 2010; Arborelius et al. 1999; Heim & Binder 2012; Plotsky et al. 1998). Prior research has reported

that depressed patients and individuals at high risk of depression tend to exhibit altered evening cortisol concentrations and cortisol awakening responses (CAR). For instance, elevated levels of evening cortisol have been reported to be characteristic of major depressive disorder (MDD) in both adolescents (Angold 2003; Dahl et al. 1991; Goodyer et al. 1996) and adults (Gold et al. 1988; Plotsky et al. 1998; Young et al. 1994). Similarly, higher CAR levels have been associated with a heightened risk of developing MDD. Cross-sectional studies have previously reported positive associations between CAR levels and depressive symptoms (Dahl et al. 1991; Pruessner et al. 2003). Although not all depressed patients display HPA axis dysregulation (Heim et al. 2008), these alterations in diurnal cortisol rhythms are understood to influence depression in part as a result of inflammation caused by glucocorticoid receptor insensitivity (Miller et al. 2009) and impairment of glucocorticoid-mediated negative feedback processes of the HPA axis (Pariante & Lightman 2008). Thus, prior research has emphasized that changes in the HPA axis are not only affected by the embodiment of early life social experiences but may also predict individual risk for depression later in life.

These studies, however, have mostly been reported among Western and industrialized populations, where cultural, economic, and psychosocial environments vary in comparison to low- and middle-income contexts, such as that of these research findings. Testing this pathway in diverse populations is necessary to assess the generalizability of the effects of early life social experience on downstream health outcomes and to identify the factors that may drive psychopathology. Additionally, the longitudinal design of this study allows us to explore the durability of the effects of early life conditions on HPA axis function, as only a small handful of studies have tracked the impacts of early life stress prospectively. Numerous scholars have made

the call for further longitudinal studies on HPA axis function for these reasons (Tarullo & Gunnar 2006; Heim et al. 2008; Koss & Gunnar 2017).

Our aim here is to evaluate the role of early life stress as a predictor of adult depression, including the possible mediating role of the HPA axis as an underlying pathway in a non-clinical, naturalistic setting. Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a longitudinal population-based birth cohort study located in metropolitan Cebu, Philippines (Adair et al. 2011). Previous research in this sample has reported dramatically higher rates of depression among individuals who witnessed domestic violence growing up (Hindin et al. 2006) and that socioeconomic status across the lifecycle predicts altered adult diurnal cortisol rhythms (DeSantis et al. 2015). We build on this work to test the hypothesis that early life stressors will predict depression during early adulthood. Additionally, we hypothesize that altered HPA axis function, as reflected by variable bedtime cortisol and cortisol awakening response levels, mediate the depressive effects of early life stress.

6.2 Methods

Study population and data collection

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing, population-based birth cohort study of mothers and their infants born in 1983-1984 in Cebu, Philippines (Adair et al., 2010). A single stage, random clustering sampling procedure selected 17 urban and 16 rural communities (barangays) among the 243 barangays in the metropolitan Cebu area, resulting in the recruitment of 3327 pregnant women. Initial and follow-up surveys were conducted through question-based, in-home interviews. Data for this paper come from survey rounds conducted in 1991-1992, 1994-1995, 1998, 2002, and 2005. All

interviews were completed in Cebuano. Excluding participants with highly atypical sleep patterns (Mastorakos & Ilias 2000), complete socio-demographic, psychosocial, mental health, and cortisol data were available for 1244 participants. Comparisons of our analytic sample with the larger cohort sample from the 2005 collection not included in this analysis show non-significant differences in household income at birth 2005, the frequency of sibling death, and depression severity (all $p > 0.3$). Conversely, education levels at 2005 ($p = 0.0067$) and assets at 2005 ($p = 0.0398$) were higher in the analytical sample, while maternal absence ($p = 0.00001$) and paternal absence ($p = 0.00001$) occurred more frequently in the excluded sample. The analytical sample tended to witness parental violence at a greater proportion ($p = 0.075$). Thus, while the analytic sample is still sizable, this analysis cannot be generalized to the larger CLHNS cohort. This research was conducted under conditions of written informed consent with human subjects clearance from the Institutional Review Boards of the University of North Carolina, Chapel Hill, and Northwestern University.

Measures of early life stress, parental support, and depression

Early life stress variables included measures of maternal absence, paternal instability, sibling death, and witnessing domestic violence during childhood (Gettler et al 2015; Hindin & Gultiano 2006). Participants were classified as having experienced maternal absence if they lived in a separate household than their mother at 8.5 years old in 1991 or 11.5 years old in 1994. Individuals who were classified as having experienced "paternal instability" were those whose father were deceased or absent, whose mother was unmarried during their first year of life or beyond, or whose mother remarried during their childhood-juvenile period from birth up to age 11.5 (±0.4) years, which was in 1994. Sibling death was assessed based upon maternal reports of

her children's births and deaths from 1983 until 1994 when participants were 11.5 years old, also in 1994. Finally, participants during the 2002 data collection wave (17-19 years of age) were asked “Do you remember if either of your parents/caretakers ever hit, slapped, kicked, or used other means like pushing or shoving to try to hurt the other physically when you were growing up?” All four early life stress variables were operationalized as dichotomous categorical variables and also analyzed as a composite variable. These variables were among the small handful of data points on early life stress that were collected during the study, which was initially designed to study the long-term health impacts of infant feeding.

In addition to evaluating the effects of social adversity on depression later in life, we evaluated the potential buffering effect of positive social experiences as reflected in a measure of parental support. Prior research has reported better mental health outcomes during adulthood when children experienced various forms of parental care-taking (Duan et al. 2016; Hostinar et al. 2014). Social support measures were similarly limited and consisted of two variables that measured parental support, specifically questions that asked whether the participant felt close to one’s mother and father during childhood during the 2002 data collection when children were 17-19 years old (Hock et al. 2016). Domestic violence questions were administered in 2002 as well. Whether an individual witnessed domestic violence and felt close to one’s parents were retrospective reports of the individual’s experience growing up, while measures of maternal absence, paternal absence, and sibling death were assessed at the time of data collection.

Depression was measured using an adapted version of the Center for Epidemiologic Studies Depression Scale (CES-D), which is a commonly utilized mental health battery used to screen for depression and assess depressive symptomatology (Radloff 1977). The CES-D was administered during the 2005 data collection wave for the CLHNS when participants were 21-22

years old. This depression screener queries both negative (e.g. difficulty eating and sleeping, feeling lonely, suicidal thoughts, etc.) and positive experiences (e.g. feeling happy, hopeful about the future, enjoyed daily activities, etc.). Ratings on a three-point scale ranged from 'none of the time' (1), 'occasionally' (2), to 'most or all of the time' (3). Scores were summed across all 16 questions, following reverse scoring of positive items, to generate an index of depressive symptoms. Cronbach's α was 0.7338, suggesting a high degree of scale reliability.

Cortisol collection, preparation, and measurement

During the 2005 survey, each participant was provided with instructions and three polypropylene tubes for saliva collection. Three samples were collected: before bed, immediately upon waking, and 30 minutes after waking. Each tube was pre-labeled to avoid confusion and contamination. Participants were also instructed not to brush their teeth or smoke 30 minutes before providing any samples and were given article diaries in which they were instructed to record the date and exact time the samples were provided.

Saliva tubes were collected later the second day by an interviewer, who placed the tubes on ice packs in a cooler while in transit to freezer storage at -35C. Samples were shipped on dry ice to Northwestern University, where they were stored at -80C. They were later thawed, centrifuged, supernatant separated, and aliquoted into smaller tubes for analysis of individual analytes. Cortisol was assayed in duplicate by a laboratory in Trier, Germany, using a time-resolved immunoassay with fluorometric detection (DELFIA). The intra- and inter-assay coefficients of variation (CVs) were between 4.0% and 6.7%, and 7.1% to 9.0%, respectively. Samples with CVs over 12% were rerun. The cortisol awakening response was calculated by

subtracting the AM cortisol values from the levels 30 minutes later. All cortisol values were logarithmically transformed to correct strong positive skews.

Covariates

All analyses were adjusted for sex, household income at the 2005 data collection, a household assets scale, and time of saliva collection (Kudielka & Kirschbaum 2003). To control for the effects of recent stress, self-reported psychosocial stress experienced within the last month was quantified via a modified version of the 10-item perceived stress-scale (PSS) (Cohen et al. 1994). To ensure cultural appropriateness, all stress related questions were pilot tested and refined in focus groups. Participants were asked to rate on a five-point scale (0 = never, 4 = very often) how often they experienced a particular form of stress. The PSS was administered in Cebuano, after being translated from English and back-translated to confirm accuracy. As a result of preliminary research with the PSS in Cebu, prior to implementation in the 2005 survey, two questions (item 9, "how often have you been angered"; item 10, "how often have you felt difficulties were piling up") were replaced with two new questions: "In the last 4 weeks, how often have you dealt successfully with irritating life hassles?" and "In the last 4 weeks, how often have you felt that you were effectively coping with important changes that were occurring in your life?" Scores were summed across all 10 questions, following reverse scoring of six positively stated items.

Data analyses

All analyses were conducted using version 13.1 of Stata (Stata Corporation, College Station, TX). Depression scores, PSS, waking cortisol (nmol/L), bedtime cortisol (nmol/L), and household income were all analyzed as continuous variables. The data analysis plan consisted of

four stages. First, bivariate associations between early life stress and depression scores were calculated. Second, we considered sex and household income and the number of household assets as predictors. Third, we added measures of feeling close to one's mother and father to evaluate the hypothesized protective role of social support. Our final model assessed the role of the HPA axis by including measures of PM cortisol and the cortisol awakening response, both of which were adjusted for time of saliva collection. $\alpha < 0.05$ was used as the criterion for statistical significance.

6.3 Results

Nearly half of all participants reported witnessing domestic violence in their household while growing up (Table 1). A smaller proportion of respondents had a sibling die during childhood, experienced maternal absence, or faced paternal instability. In contrast, a substantial majority of participants felt close with their mother or father. The average CES-D score in the analytic sample was 23.4/48.

Our first model assessed the relationship between our early life stress measures and adult depression (Table 2). Of the four measures of early life stress, witnessing parental violence and experiencing a sibling death during childhood significantly predicted depression at age 21-22 and increased an individual's depression score by an average of 0.86 and 0.63 points, respectively, in fully adjusted models ($p < 0.0001$) (Figure 1). No other early life stress measures significantly predicted depression. Additionally, we find that males are at lower risk of experiencing depressive symptoms compared to women.

We then controlled for possible effects attributed to socio-economic status and educational status by adding measures of household income, the number of household assets

during 2005, and educational attainment. After controlling for income, assets, and education level, the relationship between witnessing parental violence and depression is weakened but remains significant, while the effect of a sibling's death during childhood was no longer statistically significant after adjustment. Females were more likely to be depressed. Number of household assets was negatively associated with depression scores while the relationship between household income and depression approached significance.

Next, we included measures of parental support. The relationship between witnessing parental violence and depression becomes marginally attenuated after controlling for parental support variables. The relationship between feeling close to one's mother and adult depression was not significant but the association between feeling close to one's father and depression was significant ($p = 0.039$). On average, feeling close to one's father corresponded with lower depression scores (Figure 2).

Our last model assessed whether early life stressors predicted alterations in HPA circadian dynamics, and if so, whether these might mediate relationships between early experiences and adult depression. Specifically, we tested the relationship between adult depression and bedtime cortisol concentrations and the cortisol awakening response. Bedtime cortisol levels at age 22 predicted higher levels of depression ($p = 0.002$) (Figure 3). The effect of the cortisol awakening response did not reach significance. Notably, including the cortisol variables modestly strengthened the relationship between witnessing parental violence and depression as indicated by the increase in the coefficient of the witnessing parental violence variable from Model 3 (0.76) to Model 4 (0.80). Additionally, those who witnessed domestic violence during childhood exhibited significantly lower levels of bedtime cortisol (Figure 4).

Finally, to explore the cumulative impact of stress during child development, we created a composite variable of early life stress by combining all four stress variables and reassessed the same models as discussed above (Table 3). The early life stress composite measure remained significantly associated with adult depression after controlling for socioeconomic status, parental support, and cortisol variables. Additionally, the same covariates (e.g. sex, educational attainment, feeling close to one's father, and bedtime cortisol levels) significantly related to depression as those analyzed in the models that explored the independent effects of each early life stress variable on depression (Table 2).

6.4 Discussion

Our findings suggest that witnessing domestic violence during childhood predicts the severity of depressive symptoms and alterations in HPA axis function during adulthood in Cebu City, Philippines. However, contrary to previous findings in the literature, these relationships appeared to be independent as indicated by the strengthened relationship between witnessing domestic violence and adult depression after controlling for HPA axis measures (Table 2). In addition, we found modest evidence for a protective role of paternal social support against adult depression among individuals who witnessed domestic violence during childhood. Considering these findings together, we conclude that witnessing domestic violence and diurnal cortisol rhythms independently predict adult depression during early adulthood, specifically during ages 21-22. Furthermore, we report that diurnal cortisol activity does not affect adult depression as a result of witnessing domestic violence during child development.

Our findings linking early life stress and diurnal cortisol rhythms with depression are in general agreement with past work investigating similar questions. We confirm the overall

positive association previously reported between early life stress and adult depression (Heim & Binder 2012; Taylor et al. 2011) as seen by the direct relationship between witnessing domestic violence and adult depression (Figure 1). None of our additional measures of early life stress, however, significantly predicted depressive symptomatology. While these risk factors were non-significant in our analyses, the deleterious effects of parental and sibling absence on mental health have been widely documented in the literature. Individuals who experienced parental loss, defined as either a prolonged absence or death of a parental figure, during childhood were more likely to report future onset of symptoms of adult psychopathologies including depression and generalized anxiety disorder (Kendler et al. 1992; Tyrka et al. 2008) and exhibit signs of HPA axis dysregulation (Breier 1989; Luecken 1998; Luecken 2000; Meinlschmidt & Heim 2005; Nicolson 2004; Tyrka et al. 2008). Similarly, experiencing the loss of a sibling during adolescence was significantly associated with symptoms of anxiety and depression during mid-adulthood among individuals who lost a sibling to cystic fibrosis (Fanos & Nickerson 1991), though the literature on the long-term impacts of sibling loss is sparse. Further research may uncover potential sources of buffering against the long-term mental health impacts of parental and sibling loss and explain the wider lack of association between early familial loss and adult depression in metropolitan Cebu.

Our results also report that adult bedtime cortisol levels, but not concentrations of the cortisol awakening response, are directly associated with adult depression (Figure 3). The positive association between bedtime cortisol concentrations and adult depression is consistent with previous studies (Gold et al. 1988; Plotsky et al. 1998; Young et al. 1994). Prior research has also reported altered cortisol awakening responses among depressed individuals. These findings tend to report elevated cortisol awakening responses during depression (Bhagwagar et

al., 2003; Pruessner et al., 2003), although negative associations have also been reported (Stetler & Miller 2005; Ellenbogen et al. 2006; van der Vegt et al. 2009). Variations in the neuroendocrine profiles of depressed patients across studies may relate to the severity of depression considered in each study, which ranges from heightened depressed mood within the normal range of symptomatology to major depressive disorder (Chida & Steptoe 2008).

We also find that individuals who witnessed domestic violence during adolescence tended to have lower bedtime cortisol levels at age 21-22, while there were no differences in the cortisol awakening response. Although many studies have reported a lack of significant associations between early life stress and adult evening cortisol concentrations (Gerritsen et al. 2010; Gonzalez et al. 2009; Miller et al. 2009; van der Vegt et al. 2009), other studies have reported significant, if inconsistent, links between early adversity and evening cortisol levels. Engert et al. (2011) and Nicolson (2004) found that individuals who received low early life parental care and experienced a loss of a parent either by death or separation exhibited higher bedtime cortisol levels, while Gustafsson et al. (2010) reported decreased evening levels among women who lived in low socioeconomic status households as adolescents. Additionally, studies on the early life impacts on the cortisol awakening response tend to report positive relationships. For example, individuals exposed to an array of stressful life experiences during child development such as parental loss and child maltreatment (Gonzalez et al. 2009) and neglect and abuse (van der Vegt et al. 2009), and adverse social conditions such as low socioeconomic status (Gustafsson et al. 2010) generally exhibited heightened cortisol awakening responses compared to their respective comparison groups. Nonetheless, several studies have reported opposing or non-significant findings (Miller et al. 2009). Similar to our prior consideration with depression, differences in the early life stress-HPA axis relationship seen across these studies may be

explained by the particular qualities of early life stress in question, such as the frequency, severity, and social meaning of the psychosocial stressor or environmental condition (Fogelman & Canli 2018; Lyons & Parker 2007; Miller et al. 2007).

Previous findings from CLHNS reported the predictive effects of witnessing domestic violence during child development on adult depression (Hindin & Gultiano 2006). This study confirms the positive relationship between witnessing domestic violence and adult depression and expands the scope of stressful experiences that occurred between birth and late adolescence to include three additional measures of psychosocial stress, which include the absence of one's father, the absence of one's mother, and the death of a sibling. This study further emphasizes the role that early life experiences have on shaping the HPA axis in this sample. DeSantis et al. (2015) reported that chronically low socio-economic status from infancy to early adulthood predicted diurnal HPA axis rhythms in adulthood. The direction of the relationships between both measures of early life adversity and depression, however, were opposing. Cumulative economic strain from prenatal development to early adulthood was associated with higher bedtime cortisol levels, lower CARs, and other characteristics of HPA axis dysregulation (i.e. lower total cortisol output, flatter cortisol slopes) while our findings show that witnessing domestic violence predicted lower bedtime cortisol levels. As previously mentioned, the nature of the stressor in question may explain the varying relationships between early life stress and HPA axis function seen across studies, though the lack of specificity in our survey question on witnessing domestic violence prelude us from ascertaining the particular qualities of the stressor that may explain our discrepant finding.

Considering the inverse relationship between witnessing domestic violence and adult evening cortisol levels, the finding that bedtime cortisol levels do not mediate the relationship

between early life stress and depression is expected, statistically, but conceptually perplexing. The strengthened relationship between witnessing domestic violence and adult depression after including the bedtime cortisol variable suggests that witnessing domestic violence predicts depression despite the fact that such individuals tend to exhibit cortisol levels of non-depressed individuals. These findings call for future research to identify alternative biological mechanisms that facilitates the durable effects of early life experiences on later life health. Other biological pathways that have previously been implicated in the early life stress-adult depression pathway include epigenetic (e.g. DNA methylation, histone modification), inflammatory (immune activation, gut-brain axis), and neurobiological mechanisms (e.g. neurotransmission, neuroanatomic changes).

Limitations

The first limitation of this study is our crude measure of early life stress and social support. Our variables were limited to family-level experiences and conditions that were reduced to only four dummy variables. There are likely a wide variety of stressors across multiple domains and levels of life that may have similar long-term effects on mental health and, in general, affect the body. Different dimensions of psychosocial stress, such as a more diverse set of experiences and conditions (various forms of social oppression, disease and illness experience, teratogens, etc.), chronicity, severity, and sociocultural meaning, could have distinct and varied sequelae on HPA axis function (e.g. diurnal cortisol rhythm, stress reactivity) and later life health.

The cultural relevance and psychometric validity of the depression screener used in this study (i.e. CES-D) may be another source of bias. While the Cronbach's alpha meets the threshold for

scale validity, the comprehensibility and relevance of the sub-constructs included in the CES-D may be compromised because of their lack of cultural relevance and salience. The same concern applies to other survey tools used in this study, such as the Perceived Stress Scale (PSS).

Third, our process of sampling and measuring salivary cortisol was not ideal. Cortisol data came from only one diurnal cycle of HPA axis function. Because momentary- and day-level changes in emotions and social experiences shape cortisol levels (Adam 2006), it is preferred to collect samples for diurnal cortisol across multiple days (Adam & Kumari 2009). Additionally, in order to maximize sample efficiency in this large, longitudinal sample for which home-based sample refrigeration was not available, the diurnal rhythm was first assessed at bedtime and followed into the next day. Only a single sample was used to quantify cortisol concentrations at each point in the diurnal rhythm. Finally, we did not assess mood states at the times of saliva sampling or electronically monitor compliance with sampling protocols.

6.5 Conclusion

In summary, witnessing domestic violence during child development predicted lower levels of evening cortisol and greater severity of depressive symptoms at early adulthood in this large, naturalistic, non-Western, and longitudinal sample of individuals in metropolitan Cebu, Philippines. Adult evening cortisol levels did not mediate the relationship between witnessing domestic violence, a measure of early life stress, and adult depression. These findings suggest that the long-term depressive effects of certain forms of early life stress extend to this large sample in the Philippines, and that early life stress and HPA axis function may shape adult depression through independent pathways within the body. Alternative biological and cultural pathways by which the effects of witnessing domestic violence during child development affects

adult depression should be explored to identify the underlying mechanisms that perpetuate the lasting effects of one's early life experiences.

6.6 Tables & Figures

Table 1. *Characteristics of participants, psychosocial environment, households*

Variables	n = 1244	Range
Demographics		
Sex (% female)	47.9	
Age (years)	21.5 (0.3)	20.8 - 22.4
Early life SES	-0.01 (2.7)	-5.5 – 13.3
Household income 2005 (pesos)	599.8 (891.7)	-6.19 - 16883.6
Household assets 2005 (count)	5.3 (2.0)	0 - 11
Educational attainment 2005 (year)	11.1	0 - 23
Adult SES 2005	0.02 (0.7)	-1.8 – 5.4
Early life stress		
Maternal absence (n, %)	15, 1.2	
Paternal absence (n, %)	33, 2.7	
Sibling death (n, %)	195, 15.7	
Witnessed domestic violence (n, %)	584, 47.0	
Not close with mother (n, %)	173, 13.9	
Not close with father (n, %)	326, 26.2	
Diurnal cortisol rhythm measurements		
Evening cortisol (nmol/L)	2.17 (2.48)	0.058 - 22.68
Waking cortisol (nmol/L)	7.50 (4.32)	0.21 – 61.01
Waking cortisol + 30 mins (nmol/L)	9.49 (5.08)	0.27 – 65.9
Cortisol awakening response (nmol/L)	1.95 (4.68)	-17.86 – 25.98
Depression and PSS scores		
Depression (CES-D)	9.34 (4.71)	0 - 29
Perceived Stress Scale (PSS)	19.71 (3.29)	11 - 34

Table 2a. *Zero-order correlations across study variables*

	1	2	3	4	5	6	7	8	9	10	11	12
1. Depression	1											
2. ELS index	0.1338*	1										
3, Sex	-0.2322*	-0.0972*	1									
4. Early life SES	-0.1360*	-0.0718*	0.0193	1								
5. 2005 SES	-0.1428*	-0.0943*	-0.0782*	0.6277*	1							
6. Waking cortisol	0.003	-0.0247	-0.1245*	-0.0082	-0.0163	1						
7. CAR	0.0279	-0.0154	0.0045	0.0515	0.0619*	-0.3092*	1					
8. Bedtime cortisol	0.0788*	-0.0124	0.0325	-0.0967*	-0.1055*	0.17*	0.0158	1				
9. Slope	0.0627*	0.0004	0.0961*	-0.0565*	-0.051	-0.4452*	0.222*	0.7903*	1			
10. PM time	-0.0747*	0.0544	0.0339	0.3248*	0.2971*	-0.0836*	0.0733*	0.0453	0.1765*	1		
11. AM time	-0.0274	0.069*	0.0876*	0.2308*	0.119*	-0.1457*	-0.0331	0.0167	0.0487	0.3958*	1	
12. Smoking	0.0198	0.0084	0.1375*	-0.0145	-0.0898*	-0.0722*	0.0103	0.0348	0.0573*	-0.013	0.1166*	1
13. PSS	0.1336*	0.066*	-0.1297*	0.0210	0.0476	0.0613*	-0.0439	0.0161	-0.0158	0.0667*	0.0223	-0.001

*$p < 0.05$

Table 2b. *Zero-order correlations across early life stress and cortisol measures*

	1	2	3	4	5	6	7	8	9	10
1. Parental instability	1									
2. Maternal absence	0.2568*	1								
3. Sibling died	-0.0574*	-0.0274	1							
4. Witnessing domestic violence	0.0251	0.0584*	0.0065	1						
5. Not close with mother	0.0493	0.0195	-0.0391	0.0502	1					
6. Not close with father	0.1291*	0.0347	-0.091*	0.0914*	0.30998	1				
7. Depression	0.0018	-0.0199	0.0565	0.1122*	0.0293	0.0946*	1			
8. Waking cortisol	-0.0832*	-0.0013	0.0111	-0.0231	0.0225	-0.0262	0.003	1		
9. CAR	-0.0253	0.012	-0.0309	-0.0297	-0.0036	0.0345	0.0279	-0.30928	1	
10. Evening cortisol	0.0047	0.0334	0.0534	-0.0481	0.0356	-0.0438	0.0788	0.17*	0.0158*	1
11. Diurnal slope	0.0431	0.0326	0.0341	-0.0356	0.0185	-0.0151	0.0627	-0.44528	0.222*	0.7903*

*$p < 0.05$

Table 3a. *Multiple regression models of cumulative risk composite variable predicting depression*

	Model 1	Model 2	Model 3[#]	Model 4[#]	Model 5	Model 6
Early life stress	0.47 ± 0.11***	0.4006 ± 0.11***	0.365 ± 0.12**	0.353 ± 0.12**	0.4007 ± 0.11***	0.39 ± 0.11**
1	0.69 ± 0.25**	0.61 ± 0.25*	0.68 ± 0.29**	0.63 ± 0.25*	0.61 ± 0.25*	0.57 ± 0.24*
2	1.06 ± 0.29***	0.93 ± 0.29**	0.86 ± 0.29**	0.82 ± 0.29**	0.93 ± 0.29**	0.90 ± 0.29**
3+	1.26 ± 0.42**	1.0 ± 0.42*	0.95 ± 0.43*	0.93 ± 0.43*	1.04 ± 0.42*	1.01 ± 0.42*
Sex (male)	-1.77 ± 0.21***	-1.75 ± 0.21***	-1.76 ± 0.21***	-1.67 ± 0.21***	-1.81 ± 0.21***	-1.73 ± 0.21***
Early life SES		-0.066 ± 0.049	-0.061 ± 0.05	-0.045 ± 0.50	-0.060 ± 0.21	-0.049 ± 0.49
2005 SES		-0.69 ± 0.20**	-0.74 ± 0.20***	-0.71 ± 0.21**	-0.67 ± 0.20**	-0.64 ± 0.20**
Diurnal slope[a]			0.31 ± 0.11**	0.34 ± 0.12**		
CAR[b]			0.008 ± 0.023	0.013 ± 0.11		
Evening cortisol					0.30 ± 0.11**	0.31 ± 0.11**
Waking cortisol					-0.24 ± 0.16	-0.28 ± 0.16
Time of bedtime saliva collection				-0.13 ± 0.073		-0.099 ± 0.70
Smoking				0.81 ± 0.72		0.81 ± 0.68
PSS				0.13 ± 0.032***		0.12 ± 0.031***
Intercept	23.8 ± 0.20***	23.8 ± 0.22***	23.8 ± 0.23***	24.0 ± 1.7***	24.3 ± 0.39***	25.1 ± 1.7***
Model adjusted R^2	0.0649	0.0870	0.0911	0.105	0.0921	0.104

[a] values standardized and converted to z-score; [b] values converted to z-score

To account for saliva samples that were collected within the recommended window of time for the cortisol awakening response (t = 25-35 minutes after waking) (DeSantis et al. 2010), the sample size for this model is n=1194.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3b. *Multiple regression models predicting effects of early life stress measures and diurnal cortisol on depression*

	Model 1	Model 2	Model 3	Model 4[#]	Model 5
Maternal absence	-1.09 ± 0.98	-1.31 ± 0.97	-1.30 ± 0.97	-1.58 ± 1.03	-1.36 ± 0.97
Paternal instability	0.34 ± 0.67	0.39 ± 0.66	0.37 ± 0.66	0.29 ± 0.69	0.28 ± 0.66
Sibling death	0.63 ± 0.29*	0.29 ± 0.29	0.22 ± 0.29	0.18 ± 0.30	0.19 ± 0.29
Witnessing domestic violence	0.86 ± 0.21**	0.78 ± 0.21***	0.72 ± 0.21**	0.75 ± 0.21***	0.75 ± 0.21***
Not close to mother	0.079 ± 0.30	0.083 ± 0.30	0.13 ± 0.30	0.028 ± 0.30	0.10 ± 0.30
Sex (male)	-1.77 ± 0.21***	-1.83 ± 0.21***	-1.75 ± 0.21***	-1.75 ± 0.21***	-1.81 ± 0.21***
Early life SES		-0.056 ± 0.049	-0.052 ± 0.049	-0.037 ± 0.051	-0.040 ± 0.049
2005 SES		-0.72 ± 0.20***	-0.70 ± 0.20**	-0.74 ± 0.21***	-0.67 ± 0.20**
Diurnal slope[a]				0.36 ± 0.12**	
CAR[b]				0.014 ± 0.23	
Evening cortisol					0.32 ± 0.11**
Waking cortisol					-0.28 ± 0.17
Time of bedtime saliva collection			-0.061 ± 0.70	-0.12 ± 0.73	-0.089 ± 0.07
Smoking			-.87 ± 0.68	0.73 ± 0.72	0.75 ± 0.68
PSS			0.12 ± 0.31***	0.13 ± 0.032***	0.12 ± 0.031***
Intercept	23.8 ± 0.19***	24.0± 0.19***	22.9 ± 1.63***	24.0 ± 1.7***	24.0 ± 1.7***
Model adjusted R^2	0.0668	0.088	0.0981	0.106	0.104

[a] values standardized and converted to z-score, [b] values converted to z-score

To account for saliva samples that were collected within the recommended window of time for the cortisol awakening response (t = 25-35 minutes after waking) (DeSantis et al. 2010), the sample size for this model is n=1194.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Figures

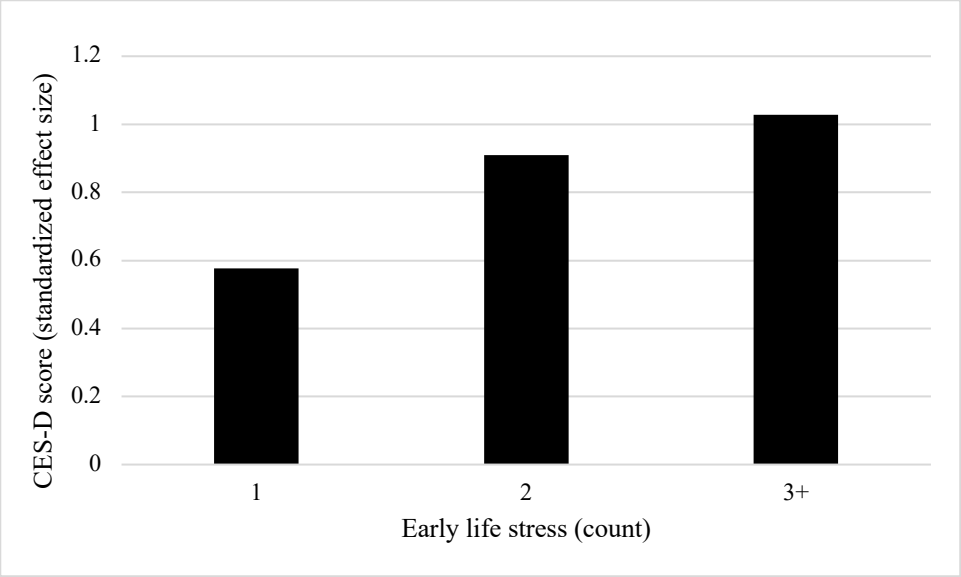


Figure 1. Effect size of early life stress groups on depression scores ($p < 0.0001$).

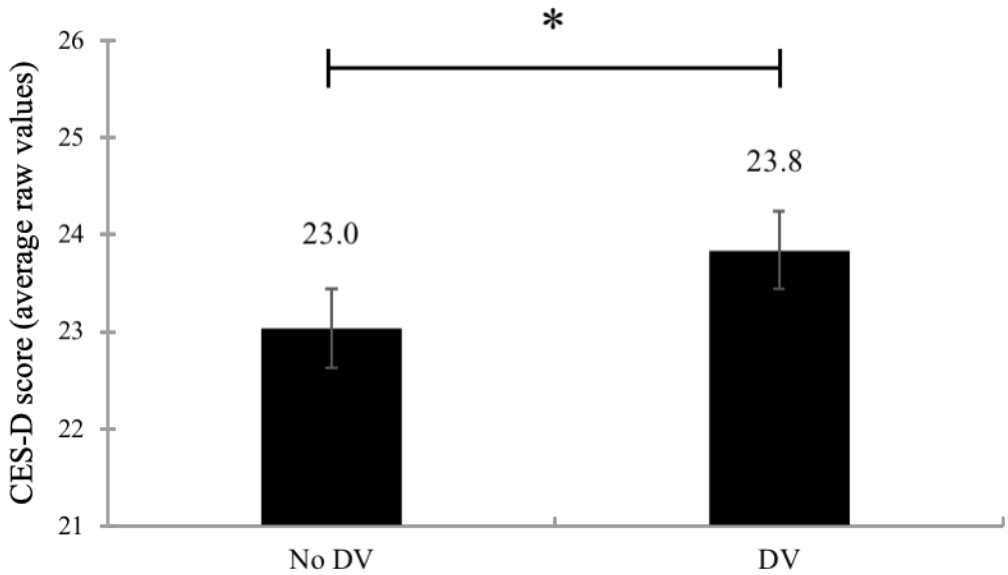


Figure 2. Mean values of depression scores stratified by past history of witnessing domestic violence ($p < 0.0001$).

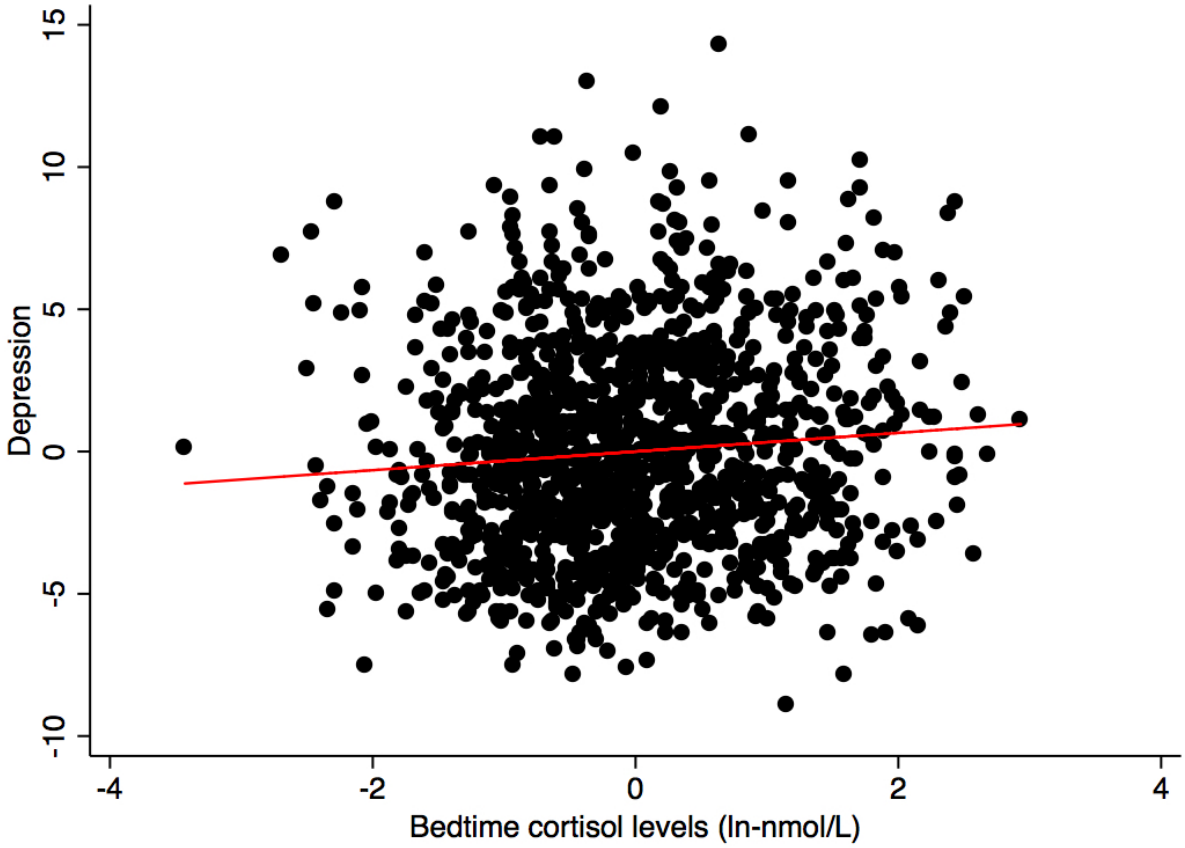


Figure 3. Partial regression plot of CES-D residual values on natural logged and standardized residuals of bedtime cortisol (nmol/L). Residuals derived from separate regressions adjusting for times of saliva collections and smoking status (p = 0.004).

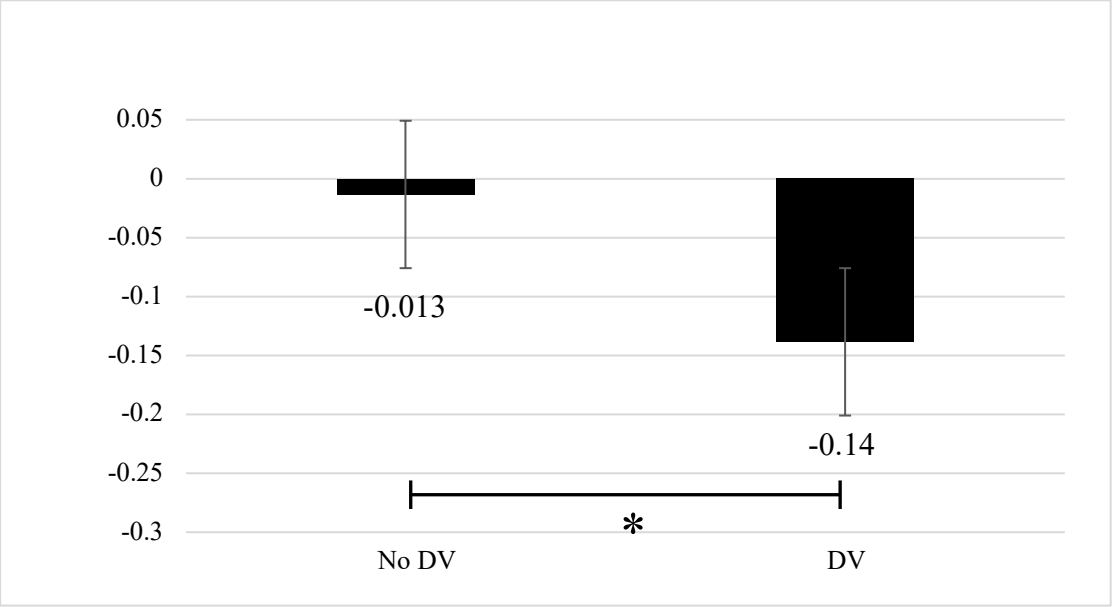


Figure 4. Average natural logged and standardized bedtime cortisol levels by witnessing domestic violence ($p = 0.018$).

CHAPTER 7: Discussion

7.1 Summary of research findings

This dissertation aimed to evaluate the long-term developmental effects of early life stress exposure - during both prenatal and postnatal development - on later life health and psychiatric disease risk across the lifecourse in South Africa and the Philippines. Building off of the growing theoretical and empirical literature on the developmental origins of health and disease, the psychoneuroendocrinology of stress, and global mental health, these three studies show that early stress and trauma exposure are important contributors to later life risk for mental illness, specifically adult depression. And while the COVID-19 pandemic interrupted my ability to assess the hypothesis I initially set out to test - whether the long-term effects of prenatal stress affected neuroendocrine function and mental illness risk in second and third generation descendants - my dissertation findings offer preliminary evidence that the lifecourse effects of early stress exposure in second generation individuals may operate through a variety of biological, socioeconomic, and developmental pathways. Here I offer a critical discussion of my findings, its contributions to the larger literature on the developmental origins of adult mental health, and its implications for public mental health in LMICs.

Chapter 4 presented evidence that greater experiences of maternal prenatal stress predicted lower offspring birthweight in the S1000 study. While the relationship only approached marginal significance ($p = 0.077$), the vast literature documenting the birthweight-lowering effect of prenatal stress exposure, and the recognized shortcomings in our measurement of maternal stress, suggest that these finding are likely biologically significant rather than due to chance. Additionally, I found that delays in fetal growth, rather than shorter gestational duration,

contributed to the inverse relationship between prenatal stress and neonatal birthweight. Considerable evidence on the maternal-placental-fetal system and fetal development suggests that maternal glucocorticoid function during pregnancy is a major pathway underlying the stress-linked alterations in fetal growth rates and gestational age and is a strong area of ongoing research. These findings contribute to the limited data on the psychosocial factors affecting fetal development and birth outcomes in South Africa and LMICs broadly, where the burden of low birthweight is the greatest.

Chapter 5 described the long-term impacts of prenatal stress exposure on late adolescent psychiatric morbidity at age 17-18 in the Birth to Twenty study. While I report a non-significant relationship between prenatal stress and adolescent psychiatric morbidity, the long-term psychiatric effects of prenatal stress were most apparent after including an interaction between prenatal stress and recent household stress, a key example of the stress sensitization hypothesis and the developmental origins of later life mental health. I also illustrate that children born to younger and primiparous mothers exhibited direct associations between greater prenatal stress exposure and GHQ scores. Additionally, maternal experiences of social support during pregnancy did not protect against the long-term mental health impacts of prenatal stress in this sample. These results contribute to the nascent literature on the long-term impacts of prenatal stress in late adolescents, particularly in LMICs, and the developmental pathways of stress sensitivity and poor mental health.

Finally, Chapter 6, a comparative study of early life stress in Cebu, Philippines, found that greater levels of early life familial stress strongly predicted greater adult depression at ages 21-22 in a dose-response fashion. Additionally, flatter adult diurnal cortisol rhythms were cross-sectionally associated with worse depressive symptoms, yet early life stress did not predict adult

cortisol function. Furthermore, when disaggregating the diurnal slope measure, adults with elevated bedtime cortisol concentrations exhibited more severe depressive symptoms. In sum, these results are consistent with the developmental origins of adult depression framework and do not suggest that HPA axis function influences the long-term effects of early life family stress on adult depressive symptoms in this sample of Filipino adults.

Together these three studies highlight the important role of early life stress exposure—both prenatal and postnatal—in exacerbating future physical and mental illness risks across the lifecourse. Greater maternal exposure to interpersonal, familial, social, and economic trauma during pregnancy in Soweto, South Africa and family-based childhood social adversity in Cebu, Philippines both served as risk factors for poor health outcomes later in development. On the other hand, across the three studies, the roles of socioeconomic status in influencing the different stress-health relationships varied and there was conflicting evidence to support the specific sensitive periods that may disproportionately shape future biological function, developmental status, and health risks later in life. Notably, all three studies derive from prospectively designed birth cohort studies in low- and middle-income contexts where the prevalence of LBW and mental illness are greatest and access to healthcare resources and public mental health policies are limited. In the following sections, I will describe and connect the contributions of my dissertation findings to the broader literature on the developmental origins of stress physiology and mental illness, reflect on the remaining research gaps in this field, and discuss future plans for research based on the findings from this dissertation.

7.2 Contributions to DOHaD, stress physiology, and biological anthropology

Developmental plasticity of early stress exposure

The lasting developmental effects of both early stress exposure on biological function, human phenotype, and disease risk reported in this dissertation extend the growing literature on stress and human developmental plasticity in biological anthropology and the developmental sciences (Kuzawa 2020; Mulligan 2016). Biological anthropologists and human biologists have long been interested in developmental plasticity as a means of adjusting to environmental variation (Boas 1912; Frisancho 1993; Lasker 1969). The emergence of sophisticated stress-sensitive ontogenetic structures throughout evolution - like the HPA axis and many others - has allowed organisms to alter their developmental processes over the lifecourse and in some contexts, adapt to ecological settings (West-Eberhard 2003). Contrary to clinical perspectives of the effects of stress on health, stress exposure is an essential and requisite socio-environmental input for basic growth and development across taxa. Researchers have become increasingly interested in exploring these intergenerational mechanisms of stress between the parent and offspring and, notably, have found a wide range of variation in postnatal offspring phenotype, such as those reported in this dissertation.

The results of this dissertation collectively examined whether early developmental stress can indeed shape one's future phenotype across their lifecourse, including birthweight (Chapter 4), adolescent psychiatric risk (Chapter 5), and adult cortisol and depression (Chapter 6). Significant evolutionary influences may play a role in explaining the unknown underlying mechanisms of the intergenerational effects of stress on phenotype, health, and biology. While I cannot determine the adaptive potential of the long-term effects of prenatal and early life stress, identifying the numerous biological and developmental processes that underlie stress-based developmental plasticity will allow anthropologists and other scientists to uncover how environmental conditions may have shaped human biology and development throughout human

evolution. My dissertation suggests that the developmental effects of stress could contribute to altered physical and mental health outcomes across the lifecourse.

Chapter 6 also confirms the developmental effects of stress on later-life mental health outcomes, specifically depression, in a non-Western middle-income context in the Philippines. Additionally, this chapter conflicted with the broader trend in the literature on the developmental neuroendocrine effects of early life stress and found that greater family-based stress during childhood did not affect adult HPA axis function at 21-22 years. My findings emphasize the importance of the postnatal childhood period as an important developmental timeframe for influencing adult mental health, specifically adult depressive symptoms. The durable nature of these phenotypic effects traces to the developing body's heightened sensitivity to environmental exposures during "critical" or "sensitive" periods, which typically take place during early windows of development (Zeanah et al. 2014). However, contrary to expectations, these findingsprovided no evidence for a potential developmental effect of stress on HPA axis function.

The null finding between early life stress and adult HPA axis function may suggest that the developmental plasticity of the HPA axis is not influenced by early family stressors in this sample. Limitations in the data, however, weaken the ability to determine the long-term neuroendocrine impacts of early life stress. First, the CLHNS data included limited measures of environmental adversity, which also prevented me from assessing a wider variety of early life adversity outside of family-related stress. Second, while the cortisol data only consisted of one diurnal cycle, the long-term impacts of early life stress on HPA axis function could also operate through alterations in cortisol regulation or reactivity and not detected through our limited measures of circadian rhythm. Finally, there were limited social experience data available in

adulthood, which precluded inclusion of other potential confounders such as recent stress. While we do not know whether the phenotypic changes caused by stress-linked developmental plasticity are adaptive (Bogin 2007; Ellison et al. 2007; McKerracher et al. 2020), researchers have widely suggested that the mechanisms of developmental plasticity can impact human health and biology and potentially lead to pathology (Wadhwa et al. 2009). This may be the case for the relationship between early life stress and adult depression found in the CLHNS cohort. Further research is necessary to elucidate the extent to which these durable effects of postnatal stress cause non-adaptive changes in human phenotype or can alter fitness outcomes.

Chapters 4 and 5 expand the limited literature on the long-term effects of maternal gestational stress on birth and late adolescent outcomes and suggest that fetal exposures may impact developmental plasticity in the next generation. Chapter 4 shows the inverse relationship between prenatal stress and birthweight corroborates the broader literature, which reports that greater first trimester prenatal stress consistently predicts lower birthweights (Coussons-Read et al. 2012; Dancause et al. 2011; Ryu 2019; Vrijkotte et al. 2009; Zhu et al. 2010). For instance, one large study of Chinese mothers and infants found that self-reported stressful life events experienced during the first trimester predicted lower birthweights, while stress during the second or third trimester was not associated with birth outcomes (Zhu et al. 2010). Additionally, Chapter 5 highlights that the residues of prenatal stress may extend into late adolescence and early adulthood.

The timing-specific effects of maternal psychosocial stress are understood to be influenced by the degree of fetal cortisol exposure, which is largely driven by the maternal-fetal-placental unit. As discussed, maternal stress exposure during earlier windows of gestation may lead to decreases in birthweight due to changes in fetal cortisol exposure as a result of increased

trans-placental exposure to maternal circulating cortisol, possibly due to a downregulation of cortisol-shielding enzymatic mechanisms, and reduced stress reactivity across pregnancy. These processes are understood to contribute greater fetal cortisol exposure during earlier stages of gestation, which in turn may influence fetal growth restriction and earlier parturition (D'Anna-Hernandez et al. 2012; Glynn et al. 2001). Despite growing evidence that supports this hypothesis of stress timing, cortisol exposure, and low birthweight status, fewer studies report null findings (Jacobsen et al. 1997; Peacock et al. 1995; Sheehan 1998). While the S1000 analysis did not assess the effects of stress at other timepoints, my results do suggest that greater maternal stress during the first trimester corresponds with lower birthweights. Additionally, preliminary results from the Birth to Twenty analysis in Chapter 5 show a significant, inverse association between prenatal stress (retrospectively reported during the third trimester from the past 6 months) and birthweight, but a forthcoming analysis with data from the entire cohort will fully assess this effect. Further studies that include multiple measures of gestational stress throughout pregnancy and fetal growth data are necessary to investigate the timing effects of stress on birthweight and untangle the proximate mechanisms that contribute to low birthweight.

Evolutionary-developmental perspectives may help explain the reasons behind the close relationship between prenatal stress and birthweight. The parent-offspring conflict hypothesis suggests that mothers and fetuses will have discordant views about the optimal trade-off between the quantity and quality of her current and future children - specifically, the maternal resources she will allocate between her current fetus and her future children (Trivers 1972, 1974). Because the mother is equally invested in each of her children, it is in the mother's genetic interest to the most optimal balance between the benefit to the existing fetus and the cost to its existing or future siblings. In contrast, the fetus, who only shares half their genes with their mother and a

quarter of genes with their past and future siblings, prioritizes the provision of maternal investment and resources towards their own survival and development. In turn, the effects of maternal investment during gestation is a possible contributor to the long-term impacts of prenatal experiences (Berghanel et al. 2017; Peacock 1991; Wells 2018). While the parent-offspring hypothesis provides a useful framework to understand the relationship between greater prenatal stress and child phenotypes across the lifecourse, more data on maternal experience and child outcomes are needed to properly evaluate these various maternal-fetal developmental strategies during gestation.

While a wide range of severity and types of maternal stress have corresponded with low birthweights and adolescent mental health (e.g. pregnancy-related distress, natural disasters, domestic violence, poverty, trauma, etc.), the precise stress-sensitive physiological processes that underlie fetal developmental plasticity and shape both low birthweight status and future behavior are also not well known (Walsh et al. 2019). As previously mentioned, a complex interaction between maternal biology, placental function, and fetal biology is understood to alter circulating levels of cortisol in the fetal environment and alter the growth, development, and health of the gestating fetus. Nevertheless, numerous stress-sensitive gestational processes implicated in shaping fetal development are currently under investigation, including the diverse roles of placenta, maternal stress sensitivity during pregnancy, *in utero* vascular function, inflammation, and glucocorticoid signaling (Dunkel Schetter 2011; Rosa et al. 2019; Ryu 2019; Wadhwa et al. 2011). In regard to elucidating the physiology of birthweight, further studies that assess fetal growth trajectories in relation to multiple measures of maternal stress are necessary to untangle the diverse proximate mechanisms that contribute to low birthweight. The numerous long-term effects of low birthweight on health and biology across the lifecourse emphasizes the need for

future evolutionary, developmental, and biological research on fetal developmental plasticity (Morsing et al. 2011; Mulligan 2016; Kuzawa 2020; Singh et al. 2013).

Chapter 5 supports interesting and fairly new evidence for prenatal stress-linked developmental plasticity during late adolescence/early adulthood and the stress-sensitization hypothesis (Hammen et al. 2000). The stress sensitization hypothesis proposes that the risk for adult mental illness following stressful life events is higher among individuals with a history of developmental trauma than among individuals without a history of developmental trauma. To date, DOHaD researchers have found evidence for early adversity-linked stress-sensitization across the lifecourse, where yet the majority of these studies have examined the impact of early life postnatal stress during childhood (McLaughlin et al. 2010; Heim et al. 2019; Müller et al. 2019, Oosterman et al. 2019). For instance, individuals with histories of childhood trauma and chronic stress across development exhibit greater risk for increased psychological stress reactivity (McLaughlin et al. 2010; Oosterman et al. 2019), heightened cortisol reactivity (McLaughlin et al. 2010; Heim et al. 2019; Oosterman et al. 2019), and elevated inflammatory profiles (Müller et al. 2019) in response to future stressors.

Growing evidence highlights the possible long-term impacts of prenatal stress on behavior and psychiatric morbidity in the next generation. While an increasing number of studies are noting the long-term impacts of prenatal stress on infant, child, and adolescent stress biology, such as the HPA axis function (Ilg et al. 2019; Koss & Gunnar 2018; Ping et al. 2020; Ziljmans et al. 2015), inflammation (Flouri et al. 2020; Glover et al. 2018), neurotransmission (Antonelli et al. 2017; Lindsay et al. 2019), and epigenetics (Barker et al. 2018; Glover et al. 2018; Provenzi et al. 2020), limited data exists on the effects of prenatal stress on *adult* stress physiology. Most research on the long-term biological impacts of prenatal stress examines the function of the adult

immune system and the HPA axis. Early research shows possible links between prenatal stress and elevated inflammatory profiles in adults (Bilbo & Schwarz 2009; Entringer et al. 2008; Plant et al. 2016; Slopen et al. 2015). Additionally, among the few studies available on the maternal prenatal stress effects on adult HPA axis function (Buchmann et al. 2014; DeSantis et al. 2015; Entringer et al. 2009), researchers found that greater prenatal stress predicted greater HPA axis function as indexed by elevated basal concentrations (DeSantis et al. 2015; Entringer et al. 2009) and greater stress reactivity (Buchmann et al. 2014; Entringer et al. 2009). Further discussion of the implications of this dissertation on elucidating the mechanisms of prenatal stress and later life mental health will follow in later sections of this chapter.

Finally, very few studies have examined the prenatal stress effects of later-life stress sensitization during adulthood. In the Avon Longitudinal Study of Parents and Children (ALSPAC) study based in Bristol, UK, Buchman and colleagues (2014) found a significant link between prenatal stress and young adult (ages 19-23) cortisol reactivity after TSST administration depending on *DRD4* (dopamine receptor D4 gene) genotype. Recent stress in the next generation did not significantly affect this relationship, though the most recent measure of stress in the young adults was a proxy variable of maternal stress when the child was 15. In one national study of childhood trauma in the United States, McLaughlin and colleagues (2010) found that greater childhood adversity predicted increased vulnerability to adult depression, anxiety, and PTSD. The magnitude of increased mental illness risk increased with the more number of adult stressful life events reported. My findings in CLHNS suggest a possible stress-sensitization effect of postnatal adversity on adult depression, and my results in BT20 show more convincing evidence on the role of stress-sensitization in influencing adolescent psychiatric morbidity as a result of increased severity of both recent stress and prenatal stress.

Implications for understanding adaptive intergenerational plasticity

Consistently moderate to high levels of prenatal stress, childhood adversity, and ongoing stress can also manifest as a larger form of chronic stress in individual's lifetime experience. Increased exposure to chronic stress is understood as a major determinant of increased immune activity (Miller et al. 2007; Gouin et al. 2008), heightened basal HPA axis activity (Fogelman & Canli 2018), disease outcomes (Cohen et al. 2012; Juster et al. 2010), and future phenotype (Evans & Kim 2013; Rohleder 2019) across one's lifecourse. In the context of prenatal development, chronic stress exposure experienced both by the parents (in their lifetime during the mother's gestation period) and the developing child could also serve as an environmental signal that is significant and reliable enough to be "heard" by the child, potentially across numerous generations. Chronic stress exposure serves as a more reliable signal due to its duration and, depending on the stressor, its magnitude and thus can more effectively communicate to the developing offspring. The longer duration of chronic maternal stress is also more likely to overlap with sensitive periods in fetal development. This overlap is conceptualized as having "the potential to facilitate the flow of more reliable, maternally derived phenotypic information that is less sensitive to such short timescale processes" (Kuzawa & Thayer 2011:225), such as transient stress exposures. As described above, stress physiological processes like the HPA axis has been widely implicated in mediating the effects of prenatal and early life stress with future offspring phenotype via stress hormones (i.e. CRF and corticosteroids), a process that has been strongly evolutionarily conserved.

The HPA axis specifically may be shaped by experiences of prior generations based on sustained intergenerationally-transmitted signals. As mentioned, there is growing evidence that

the durable neuroendocrine impacts of prenatal stress stretch across the child's lifetime, potentially into adulthood. Oberlander et al. (2008) reported that prenatal exposure to mothers with depressed and anxious mood during the third trimester was associated with increased infant cortisol reactivity as well as increased methylation of *NR3C1* (gene coding for glucocorticoid receptor). Additionally, chronic stress and war exposure predicted methylation of HPA axis-regulating genes in both mothers and infants in the Democratic Republic of Congo (Kertes et al. 2016). Both intergenerational and transgenerational epigenetic residues could serve as potential signals, among other generationally durable markers, for what Kuzawa (2005) calls "intergenerational phenotypic inertia." The development of adaptive strategies that filter out the communication of environmental variation that occurs on shorter timescales is beneficial since these environmental conditions are not accurate representations of past ecological conditions. Intergenerational phenotypic inertia could potentially circumvent this problem through reliable intergenerational signaling.

The theories and mechanisms of intergenerational adaptive plasticity are an exciting and developing area of scholarship in human biology and biological anthropology. A number of questions remain open for future consideration, including the source and direction of fetal environmental signaling (e.g. "forward"/"backward" facing), when developmental plasticity results in adaption or pathology, the exact proximate mechanisms of plasticity, and the extent to which stress-based phenotypic plasticity manifests into the lifecourse. These processes represent potentially important processes of human adaptability that allow growing individuals to alter their behavioral, developmental, and physiological trajectories across the lifecourse and ultimately influence human biological variation. As these theoretical frameworks continue, future work in human biology can continue to evaluate proposed hypothesis of human

developmental plasticity intergenerationally and across the lifecourse. In summary, findings from my three studies consistently highlight the various developmental effects of early stress exposure on physiology, behavior, and later life mental illness risk. Fetal dynamics represent important evolutionary, developmental, biological pathways that are responsive to environmental conditions through maternal signaling, and regardless of its adaptive impacts, may shape future trajectories of health and development across the lifecourse. While these three studies do not all come from a single sample or context, my findings in conversation with the broader literature suggests that prenatal and early life stress may serve as an environmental exposure important in shaping stress-related developmental plasticity in the next generation, and possibly future generations.

Mechanisms of development stress exposure, stress physiology, and later life mental illness risk

Findings from this dissertation also extend the growing literature on the developmental origins of health and disease and shed light on the long-term effects of intrauterine trauma exposure and postnatal early life stress on future psychiatric morbidity in the next generation. Collectively, these studies suggest that early life experiences play important roles in shaping biology (e.g. birthweight in Chapter 4), mental health (psychiatric morbidity in Chapter 5 and 6), and behavior (mood, stress, and psychological status in Chapters 5 and 6) across the lifecourse. While I was not able to test my original hypotheses on the role of the HPA axis in underlying the long-term effects of early stress in the BT20 sample, I was able to assess this hypothesis in a comparative analysis using longitudinal birth cohort data from CLHNS, which showed that adult diurnal cortisol rhythms did not influence the adult depressive effects of early life stress. Additionally, my findings from Soweto show evidence for a potential prenatal stress-linked developmental

pathway that affects later life mental health during late adolescence and early adulthood. In this section, I will describe the contributions of these studies to the current literature on DOHaD research on early stress exposure and mental health and propose a possible pathway by which prenatal stress intergenerationally influences child health and development and affects later life mental health status.

The birthweight lowering effect of maternal prenatal stress, along with low birthweight status generally, is becoming increasingly implicated in the long-term psychopathological impacts of the developing child, including anxiety, attention-deficit hyperactivity disorder, depression, psychosis, and schizophrenia (Ellman et al. 2019; Mathewson et al. 2017; Räikkönen et al. 2012; Schlotz & Phillips 2009; Thomas et al. 2009). For instance, a large analysis of Swedish and Danish birth registries (n = 1.49 million) report that low birthweight predicted an increased risk for anxiety disorders, substance use disorders, schizophrenia, and drug use disorders (Abel et al. 2010). Several biological pathways have been implicated in the mechanisms underlying the association between low birthweight and adult mental health. Birthweight is associated with structural and functional changes in the brain during adulthood (Buss et al. 2007; Raznahan et al. 2012; Taylor et al. 2011), which have been associated with adult depression (Ye et al. 2020) and cognitive function impairments (Bjuland et al. 2014; Farajdokht et al. 2017; Taylor et al. 2011). Additionally, low birthweight infants have exhibited greater HPA axis activity and inflammatory profiles during adulthood (Bhuiyan et al. 2011; Phillips et al. 2000).

Importantly, birthweight is not a good proxy for fetal growth and development as birth size and gestational age may be shaped by separate underlying mechanisms that may also have distinct impacts on future psychopathological risk (O'Donnell & Meaney 2017). Thus it is useful

to understand the proximate mechanisms that underlie the effects of prenatal stress on the fetus. Maternal prenatal stress exposure is understood to shape a series of complex neuroendocrine, inflammatory, and molecular pathways that alter the developmental trajectories of the fetus *in utero*. Greater maternal stress during pregnancy may result in an overactivation of a suite of stress regulatory mechanisms, which has been shown to penetrate the gestational environment and reach the fetus despite the presence of extant stress-buffering mechanisms (e.g. placental neuroendocrine and enzymatic activity, anti-inflammatory cytokines, etc.). Stress-induced alterations in the gestational environment may then impact the sensitive and dynamic biology of the developing fetus, resulting in altered function of the fetus's own stress physiology and brain development (Glover et al. 2018; Monk et al. 2019; O'Donnell & Meaney 2017).

For instance, research has shown that greater fetal exposure to glucocorticoids and inflammatory cytokines are understood to influence placental inflammatory function and neuroendocrine secretion (Hantsoo et al. 2019; Kratimenos & Penn 2019; O'Donnell et al. 2009; Sandman 2018), fetal growth trajectories (Entringer et al. 2011; Heinrichs et al. 2010; Valsamakis et al. 2020) and gestational timing (Bandoli et al. 2018; Ting et al. 2018). Recent findings has also shown that fetal exposure to maternal glucocorticoids corresponds with altered methylation profiles of infant glucocorticoid receptor (Mulligan et al. 2012; Sosnowski et al. 2018), neurotransmitter (Unternaehrer et al. 2016), neurogenesis-related genes (Braithwaite et al. 2015; Devlin et al. 2010; Kertes et al. 2017) and loci involved in placental glucocorticoid function (Conradt et al. 2016; Monk et al. 2016). Finally, prenatal maternal anxiety has been shown to predict neonatal "microstructure of regions important for cognitive-emotional function (right insula and dorsolateral prefrontal cortex), sensory processing (right middle occipital cortex), and socioemotional function (right angular gyrus, uncinate fasciculus, posterior

cingulate, and parahippocampus)" (O'Donnell & Meaney 2017:320), regions that have been consistently linked with internalizing behaviors in infants. Together, the literature suggests that these gestational neuroendocrine, inflammatory, neurobiological, and molecular mechanisms not only alter fetal biology, but may also durably persist in the postnatal life of the child.

Chapter 5 shows evidence for the possibility that greater levels of prenatal stress may sensitize the developing child to stress, and thus making the child more vulnerable to developing poor mental health outcomes like depression. As the number of retrospective and longitudinal studies on human development grow, researchers are finding that prenatal stress-induced fetal cortisol elevations and low birthweight are significant risk factors for later-life HPA axis dysregulation (e.g. flatter diurnal rhythms, increased cortisol reactivity), inflammatory function, altered brain structure, and mental illness risk in adolescence and adulthood. A recent meta-analysis also found that low birthweight was associated with increased odds of later-life depression (de Mola et al. 2014), and as I explain above, low birthweight status may be a result of maternal stress-linked increased fetal cortisol exposure, particularly during early pregnancy. In one study, researchers found that women who experienced greater maternal anxiety during pregnancy were more likely to have children with flattened diurnal cortisol slopes, which predicted depression in female adolescents (Van den Bergh et al. 2008). This growing area of research on prenatal stress is consistent with the larger body of scholarship on the effects of postnatal early life stress, another sensitive period for stress physiological function, which are known to have similar lasting effects on neuroendocrine, inflammatory, and molecular mechanisms across development, extending into adulthood (Gustafsson et al. 2010; Heim & Binder 2012; Taylor et al. 2010).

Early stress-linked dysregulation of stress physiological mechanisms, characterized by altered diurnal cortisol rhythms, glucocorticoid resistance, chronic low-grade inflammation, and altered cortical volume and brain function, has consistently been reported as both a prospective risk factor and cross-sectional neuropsychiatric phenotype of mental illness in adolescents and adults (Doane et al. 2013; Heim et al. 2019; Jarcho et al. 2013; Miller et al. 2011; Taylor 2010; Van den Bergh et al. 2008; Vrshek-Schallhorn et al. 2013). Though the pathophysiological mechanisms of depression are variable and still unknown, alterations in cortisol activity are understood to influence depression possibly as a result of inflammation caused by glucocorticoid receptor insensitivity (Miller et al. 2009) and impairment of glucocorticoid-mediated negative feedback processes of the HPA axis (Pariante & Lightman 2008). Studies also show that chronic stress-induced hypercortisolism and inflammation initiate a cascade of neurophysiological processes that alter the function of the serotonergic system (Leonard & Song 1999; Leonard 2001). The widespread impacts of these stress mechanisms may then impact the neurocircuitry of the brain, specifically the amygdala-centric circuit that modulate the emotional characteristics of depression and other psychopathologies (Krishnan & Nestler 2010; Savitz & Drevets 2009). While further research is necessary to confirm the pathophysiology of depression, strong and growing evidence suggests that stress physiological impacts of prenatal and early life stress can have durable impacts on these biological pathways that may raise psychiatric disease risk in the next generation.

The BT20 data (Chapter 5) also show that an interaction between greater prenatal stress and more recent stress exposure predicts higher psychiatric morbidity. Based on insights from the early life postnatal stress literature, there are two possible mechanisms that may facilitate the lasting impacts of prenatal stress on future psychiatric morbidity. First, as described already,

increased severity of early stress may cause durable increases in psychological and physiological stress reactivity (e.g. HPA axis, the immune system, and brain function) into adulthood, which may make individuals respond worse to future stressors, and in turn increase one's risk of developing MDD (Hammen et al. 2000; Heim et al. 2019; Kendler et al. 2004; McLaughlin et al. 2010). For instance, adults with histories of childhood trauma and chronic stress across child development tend to exhibit greater risk for increased psychological stress reactivity, heightened cortisol reactivity, and elevated inflammatory profiles in response to future stressors (Heim et al. 2019; Müller et al. 2019; Oosterman et al. 2019). Recent studies have also reported the long-term impacts of child abuse on brain function, including regions like the amygdala and hippocampus that regulate the perceptions of threat appraisal and emotions (e.g. fear, sadness) and are involved in the pathogenesis of MDD (Dannlowski et al. 2012; Opel et al. 2014; Teicher et al. 2016). These early stress-linked alterations in future stress physiology may subsequently predispose individuals to being more sensitive to future stressors, which in turn may increase an individual's risk for a suite of psychopathologies, including depression.

Conversely, greater histories of prenatal stress may increase the severity of adult depressive symptoms or MDD and increase emotional and biological sensitization to future stressors and adverse events. As seen in Chapter 6, childhood trauma, and more recently prenatal stress, are well-known risk factors that influence the severity and duration of MDD and other psychopathologies (Mandelli et al. 2015). Additionally, the major symptoms of MDD, such as persistent feelings of victimization, learned hopelessness and helplessness, and negative appraisal (Folkman & Lazarus 1986; Peterson & Seligman 1983) may have elevated one's sensitivity to and appraisal of recent stressful events in the BT20 sample. Past findings have shown that adults with histories of childhood trauma and greater MDD severity, particularly

among melancholic subtypes, have developed increased psychological (Medrano & Hatch 2005; Peterson & Seligman 1983) and neuroendocrine sensitization (Stroud et al. 2011) to future stressors. Thus, greater accounts of or sensitivity to recent stress may have arisen as a function of the depressive effects from prenatal. Future longitudinal research is needed to determine the underlying stress physiological mechanisms by which prenatal stress influences future stress sensitivity and psychopathological morbidity.

Though I did not find this in my analysis, the literature also notes potential sex-specific impacts of early life stress on HPA axis function and poor mental health, specifically in females. The long-term impacts of prenatal stress on gestational and postnatal HPA axis development and mental health have repeatedly been found exclusively or in greater magnitude in females compared to males (Glover & Hill 2012; Goldstein et al. 2019; Sutherland & Brunwasser 2018). Recent evidence shows that the female placenta reduces cortisol-inactivating 11β-hydroxysteroid dehydrogenase type 2 activity, increases cortisone-active 11β-hydroxysteroid dehydrogenase type 1, and upregulates glucocorticoid receptors, collectively resulting in greater permeability and fetal exposure to circulating cortisol in females compared to males (Clifton 2010; Mina et al. 2015). Furthermore, several studies have also reported more pronounced effects of greater maternal stress and prenatal synthetic glucocorticoid administration on increased cortisol reactivity among females (Alexander et al. 2012; de Brujin et al. 2009; Quesada et al. 2014; Van der Bergh et al. 2008) or only in females (Ping et al. 2015). For example, Van den Bergh et al. (2008) found that the mothers who experienced greater anxiety during pregnancy had children who, regardless of gender, exhibited flatter diurnal cortisol rhythms. Furthermore, the long-term neuroendocrine effects of maternal anxiety were associated with worse depressive symptoms, but this pattern was only seen in females. While we were not able to directly assess glucocorticoid

and gonadocorticoid activity, past research findings suggest that an interaction between estrogen and HPA axis hyperactivity may have influenced the increase in female adolescent psychiatric morbidity (Glover & Hill 2012).

There is growing evidence that these effects on the child HPA axis can persist into adulthood and potentially into the next generation (Brand et al. 2010; McGowan & Matthews 2018; Van den Bergh et al. 2017). Altered HPA axis function in adult women due to their own prenatal and postnatal exposure to stress, is believed to in turn have the potential to transmit similar effects to their developing offspring in utero, thus creating a multigenerational cycle of stress transmission (Drake et al. 2004; Kuzawa & Sweet 2009). Strong evidence from animal models displays discernable impacts of a variety of grandmaternal prenatal stress on second and third generation phenotypes, such as reduced body size, altered stress reactivity, and depressive-like mood (Drake et al. 2004; Ward et al. 2013). A small handful of human studies documents multigenerational effects of prenatal conditions among grandchildren, but these studies only focus on the impacts of undernutrition and rely on retrospective reporting of experience. While this dissertation was unable to assess this hypothesis due to the COVID-19 pandemic interrupting my data collection in South Africa, my results from Chapter 5 show preliminary evidence that prenatal stress may impact the stress physiology of reproductively aged adolescents and adults later in life.

7.3 Implications for public health in South Africa and the field of global mental health

It is plausible that some of South Africa's largest public health burdens both result from and perpetuate this pathway of intergenerational stress transmission. LMICs face greater burdens of poor birth outcomes and mental illness, and South Africa is no exception. Rates of low

birthweight are relatively high (14.2%) and surprisingly close to the rates observed in more poverty-stricken countries in the sub-Saharan region (UNICEF-WHO 2019). In South Africa, LBW is the second leading cause of death in children under 5 years of age (Bradshaw et al. 2003). Additionally, across sub-Saharan Africa, South Africa ranks among the highest in rates of mental, neurological, and substance use disorders. The 2016 Global Burden of Disease study estimated 12-month prevalence for any psychiatric disorder was 16.2%, or approximately 9.1 million individuals (GBDCN 2017). The economic and political legacies of apartheid continue to the present today, and through these intergenerational pathways of stress transmission, the lasting impacts of apartheid may potentially continue to reverberate across generations and sustain the social and racial health disparities in mental illness and poor birth outcomes seen today in South Africa.

These data emphasize the importance of prenatal and early childhood development programs and policies in South Africa, especially for child mental health. President Nelson Mandela's first major policy announcement during his term was to institute free healthcare for children six years and under and also for pregnant women (BMJ 1997). While the country has shown considerable progress in antenatal clinic enrollment and attendance, rates of adverse infant birth outcomes remained problematic, even to today, and research has shown major inefficiencies and strains on the public healthcare system (Damian et al. 2016; Wabiri et al. 2016). The early childhood development sector has also seen similar improvements, but limited infrastructure, capacity, funding, and training opportunities continue to stymie the efficacy of these national policies (Atmore 2013). The South African Department of Health released its most recent version of the Guidelines for Maternity Care manual in 2015 (SADOH 2015), outlining its comprehensive policies for care and delivery of newborns in the country. The Guidelines were

published in part to meet Millennium Development Goals and to also respond to the alarming rates of maternal and infant deaths in the country. The document, however, does not include details or specific information about the role of psychosocial stress and mental health in the document. Along with existing initiatives and advocacy campaigns from the NGO and public, the findings in this dissertation call for continued improvements and support for prenatal and early life development programs in order to improve physical and mental health outcomes across the lifecourse.

Findings from this study also contribute to the limited literature addressing the lifecourse determinants of mental health impacts in South Africa, particularly in longitudinal and prospectively designed studies. Given the massive societal, economic, political, and public health changes over the past 30-40 years, the conditions that influence public mental health also change (Richter et al. 2018). Additionally, there are a limited number of longitudinal studies that originate before apartheid and span over 10 years in South Africa, making the BT20 one of the few multigenerational birth cohort studies in the country and also Africa's largest and longest running study of child development (Richter et al. 2007). A number of South African birth cohort and longitudinal studies are running today, including the Drakenstein Child Health Study, the Health and Aging in Africa Study based in the Agincourt subdistrict of Mpumalanga province, and the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE) birth cohort study in Venda, yet most of these studies have started after the turn of the century. Finally, national level statistics of mental health trends, particularly those that are nationally representative, are rarely released by the national government and thus severely lacking. Birth to Twenty has and will remain an invaluable resource of public health data for both the country at-large and stakeholders across the world.

The onset of the COVID-19 pandemic also introduced new threats to South African mental health and exacerbated old, and sorely underrecognized, concerns. As of October 8, 2020, South Africa reported 685,155 confirmed cases, 17,248 deaths, 618,127 recovered people, and 4,318,514 tests conducted (Figures 1-3). While the South African response to COVID-19 was swift and assertive in surveilling, managing, and treating the disease (Abdool Karim 2020; Ogbolosingha & Singh 2020). Despite the rapid and effective public health response at the onset of the pandemic (South African COVID-19 Modelling Consortium, 2020), the inevitable economic and social ramifications of the pandemic and the national lockdown have disproportionately affected already marginalized communities the most (Arndt et al. 2020). Furthermore, recent research shows that the harsh government sanctions to adhere to COVID-19 mitigation policies, including militarization, demolitions of informal settlements, and widespread police brutality, have impacted already vulnerable communities who are unable to properly quarantine (Isbell 2020; Labuschaigne, 2020; Staunton et al. 2020), many of which have been shown to impact mental health (Kim 2020a; Kim et al. 2020; SADAG 2020). For millions of South Africans, vulnerability to COVID-19 infection and its impacts is amplified by other pre-existing adversities, such as hunger and violence, an overburdened healthcare system, a high prevalence of chronic and infectious disease, and alarming rates of poverty (55.5%) and unemployment (29%) (Docrat et al. 2019; Joska et al. 2020; StatsSA 2019).

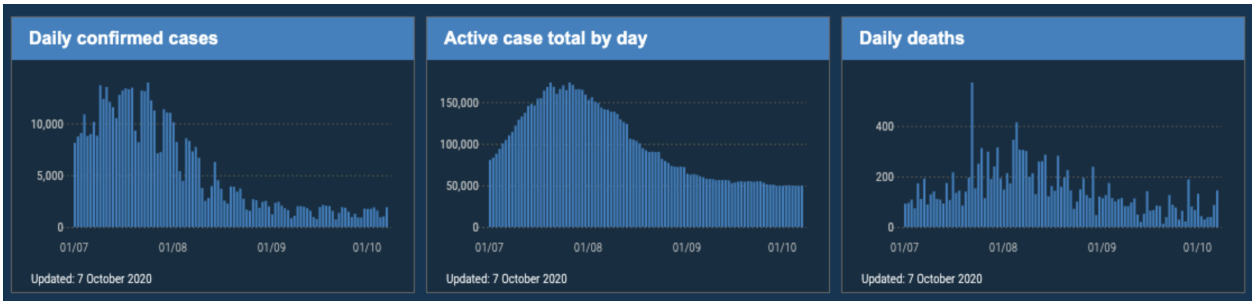


Figure 1. Daily cases, active cases, and daily deaths between July and present (October 8, 2020)

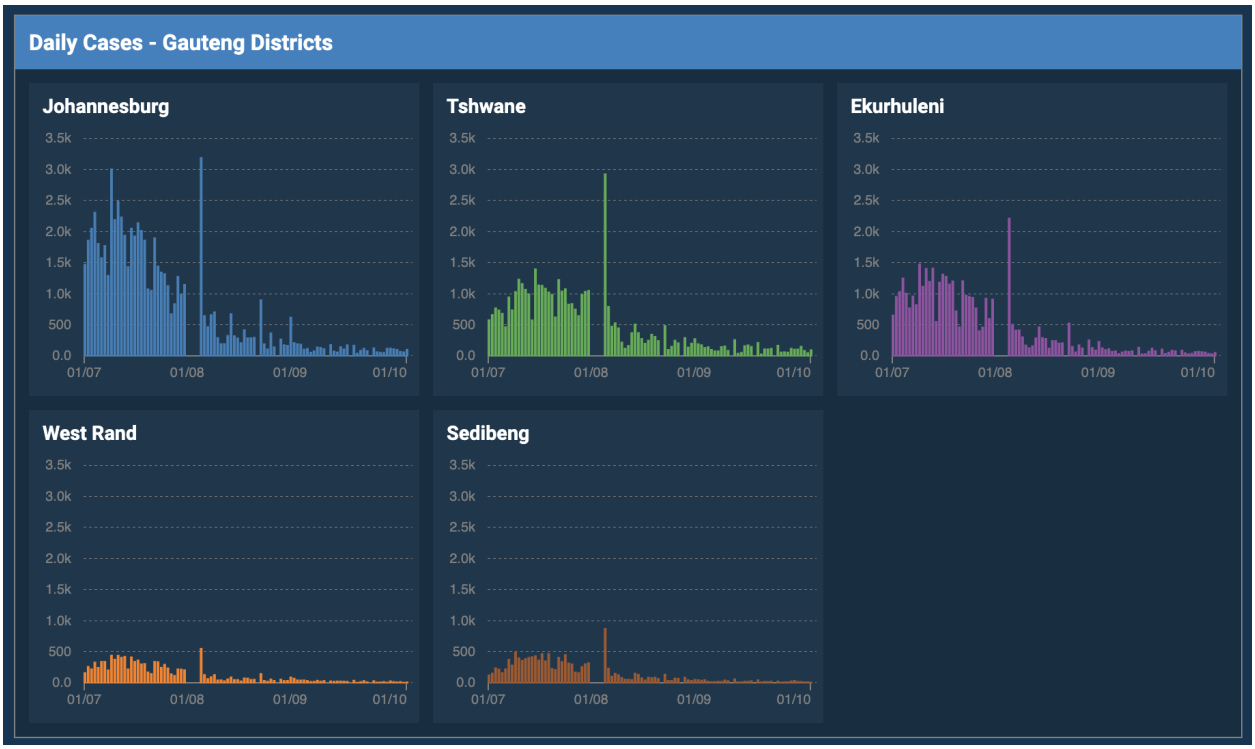


Figure 2. Daily cases in five municipalities of Gauteng

Figure 3. COVID-19 trends by subdistricts. Region D represents statistics for Soweto.

Case Study: Examining the Mental Health Impacts of COVID-19 Conditions during the First Six Weeks of the National Lockdown in Soweto

Soon after the South African lockdown, my team and I (Kim et al. 2020) quickly shifted our data collection to investigate the mental health impacts of the COVID-19 pandemic among adults residing in Soweto - a major mixed-income African city with elevated rates of comorbidities such as diabetes, hypertension, and HIV. Using an ongoing community-based epidemiological surveillance study, we combined pre-existing data on health behaviors, disease status, and social environments with telephonic survey data on perceptions of COVID-19 and mental illness risk to characterize experiences during lockdown, understandings of the novel coronavirus, and the mental health impacts of the pandemic. In a sample of 221 adults, higher perceived risk of

COVID-19 infection predicted greater depressive symptoms ($p < 0.001$; Figure 4) particularly among adults with histories of childhood trauma, though this effect was marginally significant ($p = 0.063$; Figure 5).

Greater knowledge of COVID-19 prevention and transmission was also associated with lower perceived risk of COVID-19 but higher depressive symptoms. While a large majority of participants reported that experiences of the COVID-19 pandemic did not affect their mental health (or "mind"), 10-20% of participants reported potent experiences of anxiety, fear, and "thinking too much" as a result of the pandemic. These concerns during the lockdown were driven and exacerbated by the inability to care for themselves and their families, crippling economic struggles, personal vulnerability due to illness, the invisible nature of COVID-19 transmission, and a lack of awareness of the disease. These results highlight the compounding effects of past traumatic histories and recent stress exposures on exacerbating the severity of depressive symptoms among adults living in an urban South African context.

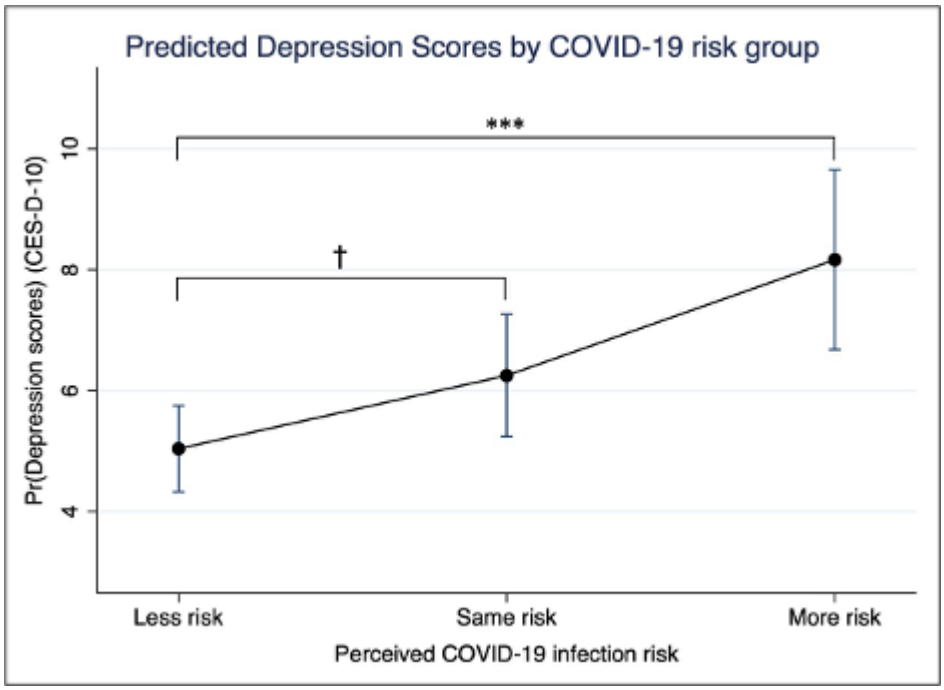


Figure 4. Predicted depression scores by perceived COVID-19 risk group (Kim et al. 2020).

Note: Greater perceived risk of COVID-19 infection corresponds with greater depression symptomatology in adults living in Soweto. The effect of being in the 'More risk' group is highly significant ($p \leq 0.001$) relative to being at 'Less risk', while the effect of perceiving that one is at the 'Same risk' of COVID-19 infection relative to other individuals living in Soweto on depression symptoms is marginally significant ($p = 0.088$).

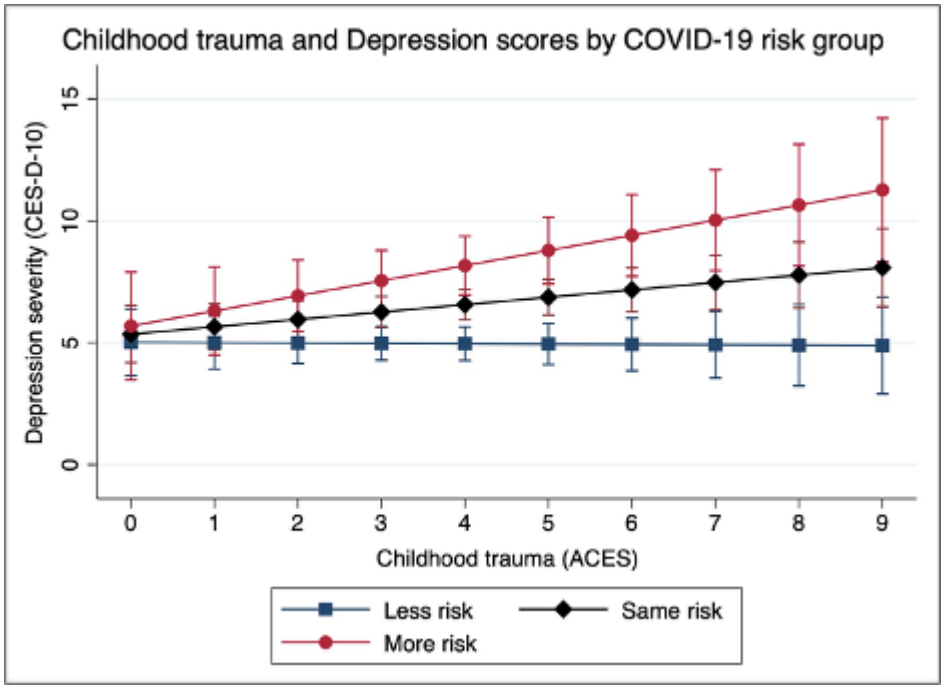


Figure 5. Childhood trauma (ACES) and Depression scores (CESD) by COVID-19 risk group (Kim et al. 2020).

Note: Greater childhood trauma (ACES) potentiates the positive relationship between greater perceived COVID-19 risk and the severity of depressive symptomatology. The effect of the interaction between childhood trauma and perceived COVID-19 risk on depression is marginally significant [$F(1,208) = 3.51$, $p = 0.0625$].

The impacts of the pandemic on tertiary care centres were dramatic, particularly during the peak of the pandemic, as hospitals were flooded with COVID-19 patients and their already full list of patients, which meant fewer available beds. The largest state hospitals were forced to turn away those whose mental illnesses were not severe enough for immediate attention (U. Subramaney & T. Mdaka, Personal communication 2020). Greater capacity of psychiatric services at the primary healthcare level could treat mentally unwell patients earlier and in turn, lessen the burden of tertiary hospitals now and in the future. These new mental health adversities exist against a backdrop of poor national support. The national mental healthcare budget is severely limited – only 5% of the national public health budget is allocated for public mental healthcare (Docrat et al. 2019). These shortages have led to overburdened clinics, difficult staff shortages, chronic medication stockouts, and in some cases, mental healthcare tragedies (e.g. Life Esidimeni Healthcare Tragedy). Reallocating funds to increase the financial capacity of psychosocial, psychological, psychiatric care is much needed. In particular, greater support of the primary-level mental healthcare is necessary. Below, I provide two promising initiatives that may assist improving and supporting future initiatives for public mental health in South Africa: telepsychiatry and stronger primary care systems.

1) Telepsychiatry

Widespread evidence highlights the therapeutic effectiveness and accessibility of phone-based counseling, particularly during public health crises and healthcare restricted settings. Telepsychiatry, or the use of telecommunications to deliver psychiatric care outside of healthcare facilities, are critical resources for high-risk and hard-to-access communities during public health emergencies. Numerous telehealth psychological interventions worldwide have shown to be cost-efficient, lead to sustained, decreased mental illness risk, confidential, and improve mental well-being, particularly public health emergencies (Bashur et al. 2016). In addition to South Africa having the highest rate of cellphone usage in the African continent (ICASA 2020), low costs, convenience, and privacy have made telemedicine a prioritized mode of healthcare delivery in South Africa (SADOH 2019). Telepsychiatry gained major attention when the WHO prioritized addressing inequities in mental health treatment (mhGAP). South Africa already has a strong platform in place that is ripe for integrating mental healthcare services - a recent priority of the National Department of Health. The South African Depression and Anxiety Group (SADAG), a vanguard in the country's response to the psychological impact of the pandemic, has provided numerous virtual counselling and referral services through telephonic and WhatsApp counselling. SADAG's call volumes have doubled since the start of the lockdown, though rural communities or individuals who lack access to the proper equipment are unable to benefit from such services.

2) Stronger infrastructure for community psychology and psychiatry

With the overall prevalence and burden of COVID-19 expected to peak in the coming months, the mental health impacts of the pandemic may also see a spillover into tertiary care centres, thus adding further pressure to the system. Diverting major portions of the case load

onto well-equipped and well-staffed community outpatient clinics can mitigate the overflow of future patients and also build an infrastructure to screen, treat, and prevent future mental illnesses. Building a stronger infrastructure for community psychology and psychiatry is multifold. This includes the development of greater home-based and non-specialty care centers for psychiatric patients situated in patients' communities, rather than 60 km away. We must also learn from the past wrongdoings of past mental health crises, in particular the Life Esidimeni tragedy which resulted in the mismanagement of the public mental healthcare system, 178 known deaths due to medical malpractice, and missing patients (Robertson et al. 2018). Greater engagement and collaboration with church leaders and traditional healers, particularly in rural settings, is also expected to improve healthcare outcomes due to South Africa's medically pluralistic context (Moshabela et al. 2017; Sorsdahl et al. 2010). Finally, greater funding for community psychology infrastructure can lay the groundwork for sustainable changes in the mental healthcare system. One interlocutor who oversees the primary mental health care system in the West Rand of Gauteng province describes the revolving door that acute psychiatric patients enter and leave throughout tertiary care settings: "...until [acute psychiatric patients] are readmitted again, they are managed by us. So I feel that the pyramid needs to shift a little bit. We almost need to put community psychiatry on top in terms of the budget" she explains.

While I have examined the effects of a variety of individual- and community-level factors across the lifecourse on adult depressive symptoms and mental health in these studies, the social and historical contexts from which many of these social and psychological factors arise are largely responsible for the current state of psychiatric morbidity and vulnerability to infection in Soweto today. Nearly all participants were born during the oppressive apartheid regime or shortly after its violent dissolution, which is when all childhood traumas reported in the original

BT20 cohort took place. Though children were not always exposed to the everyday adversities and extreme traumas of racial segregationist cultures and policies, the distributive impacts of racialized and classed violence among families often times translated to poor housing quality, food insecurity, family violence, and child abuse. The psychological, economic, and structural legacies of apartheid violence manifest in the present moment where the intergenerational trauma of apartheid may persist and sustain racial and class disparities in mental illness, socioeconomic opportunity, and infectious disease risk. We offer this history to contextualize our findings and emphasize the importance of prioritizing accessible mental health and infectious disease prevention services countrywide. We must recognize the unequal and unjust effects of trauma among marginalized communities, especially considering the historical legacies of violence in South Africa and elsewhere. Mitigating the mental health impacts of the pandemic should be a priority in Soweto given the lack of available mental healthcare services. The psychological sequelae of the lockdown may be longer lasting than expected, and greater screening, referral, and treatment options should become available. Finally, given that low- and middle-income, postcolonial communities face the greatest burdens of mental illness worldwide, the development of strong mental health research systems should be supported in these settings.

With the rise of the movement for global mental health, significant developments in scholarship, global health, and health policy have generated alongside explanatory frameworks for the prevalence and impact of psychological disease, whether implicit or explicit. Examples of such frameworks include stress and trauma based models, lack of resources such as healthcare, and biological abnormalities (e.g. imbalances of neurotransmitters in the brain). While these explanatory models have bore tremendous advancements in knowledge about the epidemiology, lived experiences, and consequences of what was previously an underappreciated set of diseases,

mental illnesses, these existing frameworks underemphasize or overgeneralize the political systems and intentions that produce the dramatic inequities in mental illness burden and undertreatment seen today. Explicit recognition and examination of the political dimensions of global mental health provide greater weight to the systems and power structures that force individuals in conditions that place them at risk of developing mental illnesses, among other morbidities, prioritize the experiences of those with mental illnesses, which include prioritizing their thoughts on risk factors, service quality, and needs, and their visions for positive mental health at multiple levels of society.

7.4 Future research

Soweto Stress Study: Intergenerational trauma, HPA axis function, and mental illness across three generations

When in-person data collection is deemed safe in Soweto, I will relaunch my original dissertation study on the intergenerational mental health effects of apartheid-based trauma on birth outcomes, HPA axis function, and mental health outcomes in second and third generation participants in BT20. Before the lockdown in late March, my study assessed mental illness risk (depression, anxiety, PTSD), stress and trauma exposure, and other lifestyle and household factors among families in and around Soweto. To trace the biological mechanisms involved in facilitating the intergenerational transmittance of trauma, I also collected saliva and blood samples to measure diurnal cortisol levels and inflammatory profiles, and to also examine how increased social support during puberty, a possible sensitive period of HPA axis recalibration, can facilitate a possible reversal of the past impacts of trauma. These new data points will be

combined with 30-years of longitudinal data to understand the life course pathways that influence the development and amelioration of later life psychopathologies.

While primary data collection is underway, my findings from Chapter 5 data have identified potential biological, developmental, and social mechanisms of intergenerational trauma. Analysis of BT20 data show that pregnant women who endured more traumatic stressors during apartheid had children who, 17-18 years after initial trauma exposure, exhibited greater psychiatric morbidity. Additionally, numerous discussions with long-time residents of Soweto, including some BT20 grandmothers and their families, in my ongoing ethnographic work corroborated these patterns and contextualized such possible biological pathways of generational trauma. Older women somberly recounted the state-sanctioned violence against their communities in Soweto during 1990 which included police killings of adults and youth, clouds of tear gas, and public executions. These violent conditions exacerbated the traumatic wounds of women who coped with domestic violence through substance abuse, men who suppressed their emotional needs and developed unrecognized mental health problems, and children who witnessed and became desensitized to such oppressive conditions, which in turn, drives future cycles of trauma and illness. My research in South Africa, however, also identifies numerous sources of healing, such as religious and community-based support, culturally competent mental healthcare, and Black empowerment, aimed at ending legacies of apartheid (Kim et al. 2019).

This study will be among the first to assess the apartheid-era effects of violence on long-term mental illness risk and the first study to identify biological pathways of intergenerational trauma and resilience through HPA axis dysregulation across three generations. Findings will contribute to the growing literature on the developmental pathways of later life psychopathology and underlying mechanisms, and may inform advancements in theory and practice within

anthropological, biological, psychological, and therapeutic fields. The study may also inform future endeavors to identify which periods of human development are optimal for intervention in order to maximize the treatment and prevention of trauma-induced mental illnesses and social complications. Understanding the temporal limits of historical trauma and clarifying its consequences across generations may also strengthen claims of redress and assist communities who have undergone historical trauma to continue to hold oppressive regimes accountable (Kim 2020b).

Reflections on the politics of intergenerational trauma

Findings on the biology of intergenerational trauma, particularly in the world of behavioral epigenetics, have already made impressionable impacts in community forums, social institutions, and governments worldwide. Evidence for intergenerational transmission of trauma was considered by The International Criminal Court (ICC) when deliberating on reparations for war crimes against Hema communities in the DRC (ICC 2017), and the California assembly passed a bill (ACR 177) to "encourage awareness that intergenerational trauma, which has been identified through epigenetic study, may have an impact on the outcomes of certain citizens of California" (Jones-Sawyer 2018). The social applications of this research, however, straddles a fine line between positive social impact and negative bioethical implications.

For example, in the case of the epigenetic inheritance, the possibility that the embodiment of impoverished or "toxic" environments (Lamoreaux 2020) could lead to durable changes in genomic expression and epigenomic profiles may reinstantiate biologically reductionist and eugenic thinking that "molecularizes" imagined social hierarchies (Meloni & Testa 2014;

Niewöhner 2011). And in some cases, this research occurs among study populations who were historically victims of social Darwinist ideology and scientific racism.

We have also seen both implicit and explicit victim blaming of research participants and in particular, vulnerable mothers, who are painted as the scapegoat for poor child health outcomes in a time where maternal exposures to trauma, teratogens, and poor nutrition are seen as a major threat to future child development (Barker et al. 2013; Richardson et al. 2014). Additionally, researchers have warned that the social malleability of hormonal and epigenetic profiles may also introduce a potential "rebiologization" of race (Duster 2015; Meloni 2017). While evidence for transgenerational epigenetic inheritance poses exciting opportunities for ongoing initiatives that aim to hold past oppressive accountable for historical violence, further research must be done before utilizing such information for reparative action.

Greater need to understand the biology of intergenerational trauma situated in the politicized and historicized context of imperialism, colonialism, racism, classism, and other forms of oppression. The work and culture of science downplays the importance of these contextual ways of thinking, and this erasure allows colonial logics to manifest in scientific knowledge production. Research occurs among study populations who were historically victims of social Darwinist ideology and scientific racism. Example - French scientist saying that we can test COVID vaccines in African countries.

Birth cohort studies have become the gold-standard method for tracing the intergenerational transmission of stress primarily due to the major focus on the developmental origins of health and disease framework in public health (Barker et al. 1989). Epidemiologists and public health officials have held birth cohort studies in high regard to elucidate the biological mechanisms underlying intergenerational trauma, as stress-related diseases such as depression

and hypertension are understood to largely originate from intrauterine exposures to maternal trauma and social adversity (Entringer et al. 2015). And throughout the twenty years of research using birth cohort studies to assess the DOHaD hypothesis, anthropologists have made substantial contributions to these research conversations with critical perspectives on the evolutionary, biological, evolutionary, social, political dynamics of the effects of early life stress and intergenerational trauma.

As research on intergenerational trauma continues, there is a growing wave of skepticism about the plausibility of these scientific findings, especially in the field of behavioral epigenetics (Miller 2010). Additionally, social scientists have raised the concern that the possibility that certain biological characteristics and behaviors could be socially malleable may feed into dangerous eugenic thinking (Meloni 2016).

Reflexivity, measurement, and reparations

Over my four years of studying intergenerational trauma in Johannesburg, three reflections continue to revisit me.

1) Ethnographic contextualization matters.

To illustrate this point, I share an entry from my field notes about my conversations with a BT20 family earlier this year:

> Thirty years after Hlengiwe took the SCS prenatal stress survey, we invited her back to SCS, this time with her 30-year old daughter, Thabile, and her 5-year old granddaughter, Thandi. The building is more than familiar to Hlengiwe and Thabile, who have been coming to our research site nearly every year for the past 30 years. When I tell them

where the bathrooms are, they laugh and correct me, telling me that I pointed them to the men's room. "The ladies' is on the top floor, *wena*!"

Hlengiwe vividly described the neighborhood violence at the time. When I asked her how she thought these conditions affected her pregnancy, she responded: "Yoh… (shakes head and looks forward). They inherited tear gas and tires and they were burning people." She then continued to explain other stressors she faced during her pregnancy: her fear of gaining too much weight, being unable to work and save money for food and clothes for her newborn, and the stigma of single motherhood.

Operationalizing a measure of "stress" during an extremely complex time of political violence and societal transition is a difficult endeavor from the start, and researchers are faced with numerous issues. First, as most epidemiological and demographic studies do, researchers either utilize internationally or locally validated measures to assess what are usually very complex social constructs or, less commonly, create their own surveys if existing scales are inadequate, though efforts to adapt scales aren't always effective (Mendenhall & Kim 2019). Second, as anthropologists have previously argued, numbers and global health metrics can flatten the complexity of lived experience and social and political realities (Adams 2016; Sangaramoorthy & Benton 2012). Meaningful histories of segregation, stigma, and political violence get erased when research assistants check off a series of likert scale responses (1-5, not concerned to very concerned), and in the context of biological studies, become simplified as concentrations of stress hormone levels, body-mass index, and cognitive function, and opening the door for victim-blaming narratives.

Third, the subjectivities of the researcher can also bias methods of data collection, statistical modeling, and what is seen as "traumatic," causing a privileging of the researcher's worldview over those of the participants. Stressors and traumas that become biologically and socially embodied and intergenerationally transmitted must first be appraised as stressful or traumatic, which is inherently a culturally-mediated process (Kohrt et al. 2009). Thus, poor assessment of psychosocial experiences like "stress" can obfuscate deep political dimensions, present missed opportunities for observing biological responses to trauma, and ultimately biasing the search for empirical "truth."

Better measurement never hurts, and for epidemiologists and public health researchers, this means engaging in deeper ethnographic theory and practice and producing reflexive scientists. Deeper ethnographic research on trauma and mental health, for example, can lead to the development of surveys that are more sensitive to the cultural realities of birth cohort study participants. For example, Kaiser et al. (2013) utilized a rigorous ethnographic approach consisting of long-term participant-observation, in-depth interviews, and focus groups to adapt existing depression and anxiety screeners and develop new mental health measures that better accounted for locally salient symptoms of distress and their negative sequelae in the Central Plateau of Haiti.

Stronger reflexive practice can also illuminate blind spots that previously obscured social or biological factors that may be involved in intergenerational stress transmission. Biocultural anthropologists are well-positioned to take the lead on practicing a reflexive anthropological process that begins with ethnography, informs epidemiological research, and in turn produces new questions for ethnographic research (Brown et al. 2009). And finally, a thorough and critical understanding of the social, political economic, and historical dynamics of intergenerational

trauma can allow scientists to more substantially contribute to public discourse on social health inequities, remembrance and memorialization, and transitional justice.

2) Is the effect of prenatal stress on later life health outcomes causal? What does this mean?

While this dissertation aimed to examine the associative relationships between prenatal stress and later-life physical and mental health outcomes using observational data, I am not able to make causal claims about the long-term impacts of prenatal stress. While this dissertation highlights the mounting theoretical and empirical evidence for the possibility that developmental stress may alter fetal and child physiological development and in turn affect their later-life health status and disease risk, my dissertation was not designed to assess the causal effects of early stress on birth weight, adolescent psychiatric morbidity, and HPA axis function, and depression and did not meet the statistical criteria for establishing causality. These include the following:

Table 6–3. The Hill criteria for inferring causation

Criteria	Definition
Strength	A strong association is more likely to be causal. The measure of strength of an association is the relative risk and not statistical significance.
Consistency	An association is more likely to be causal when it is observed in different population groups.
Specificity	When an exposure is associated with a specific outcome only (for example, a cancer site or even better a particular histological type of this cancer), then it is more likely to be causal. There are exceptions, however, for example, smoking causing several forms of cancer.
Temporality	A cause should not only precede the outcome (disease), but also the timing of the exposure should be compatible with the latency period (in non-infectious diseases) or the incubation period (in infectious diseases).
Gradient	This criterion refers to the presence of an exposure-response relationship. If the frequency or intensity of the outcome increases when an exposure is more intense or lasts longer, then it is more likely that the association is causal.
Plausibility	An association is more likely to be causal when it is biologically plausible.
Coherence	A cause and effect interpretation of an association should not conflict with what is known about the natural history and biology of the disease, or its distribution in time and place.
Experimental evidence	If experimental evidence exists, then the association is more likely to be causal. Such evidence, however, is seldom available in human populations.
Analogy	The existence of an analogy (for example, if a drug causes birth defects, then another drug could also have the same effect) could strengthen the belief that an association is causal.

Source: Hill, 1965.

Figure 6. Bradford Hill criteria for causation (Hill 1965)

The studies in my dissertation do not meet the criteria for causality listed by Hill (1965). I use the Birth to Twenty chapter as an example to assess the criteria for causality. The consistency of the finding is limited as few studies exist on the long-term mental health impacts of prenatal stress especially in prospectively designed birth cohort studies. The specificity of the relationship is also rather weak as the prenatal stress measure includes a range of heterogeneous stressors assessed by a crude “yes/no” response. The correlates of adolescent depression are multifaceted and complex, and my analyses did not account for possible mediating factors between early

stress exposure and the health outcome of interest, such as trajectories of socioeconomic status, traumatic events and health promotive experiences, for example, between 0-18 in Birth to Twenty. I also do not use experimental data or techniques in my studies, and there is a strong possibility for an analogy between past traumas from apartheid and later-life mental health consequences in children living through the post-independence and colonization era of South Africa. Conversely, the strength of the prenatal stress variable is a discernable effect size, the study design follows the temporal logic of the hypothesized pathway, the direction of the gradient is logical and confirms our hypothesis, the finding is biologically plausible based on the existing psychoneuroendocrinological literature, and the overall finding is coherent.

A number of extant concerns requires further critical reflection on the assumptions of causality in this type of observation population-based research. This includes the politically charged nature of the study of race, inequality, and biology, the risk of reductionism, and the acritical public intake of scientific knowledge (Meloni 2016). Meloni (2016; 2017) highlights the potential for an unintentional reproduction of a "biologized" and "molecularized" understanding of race through the production of scientific research that, ironically, aims to dispel eugenic, reductionist thinking and highlight the various social determinants and complexities of biological function and human health. Truth claims of biomedical and scientific findings serve as double-edge sword, leading to the production of "objective facts" and overzealous and inaccurate applications of scientific research. Philosopher of science and indigenous scholar Laurie Ann Whitt argues that the practice of "value-neutrality" allows for the work of reductionism to manifest without challenge. Value-neutrality, a key component of Western scientific epistemology claims that science is value-free, unaffected by extrinsic political, moral, ethical values. This objective disposition instills in it a sense of purity and neutrality that seemingly

grants it immunity to moral evaluation and an epistemological authority. In turn, the false promise of objectivity deflects ethical and political critiques, allowing scientific knowledge to perpetuate without challenge and consideration of other non-biomedical ways of knowing. With the already reduced view of the social environment in the broader study of the developmental origins of health and disease, psychoneuroendocrinology, and psychiatry, value-neutrality paves a clear path for the harmful biopolitical possibilities to actualize.

The Birth to Twenty study is not devoid of this risk and responsibility. As previously described, Soweto and non-White South Africans faced a long and difficult history of being the focus of eugenic technologies and interventions, scientific racism, and ongoing research – biological anthropologists in South Africa were both complicit and involved in perpetuating these violent politics. Furthermore, an answer to the primary question of this dissertation – whether and to what degree did intergenerational trauma from apartheid affect physical and mental illness risk in children over their lifecourse – poses a wide range of possible social, bio/political, and psychological consequences. These include issues of societal reckoning, retraumatization in relation to past violence from apartheid and ongoing trauma, reparations, health anxiety, and others. Moving forward, these considerations for causality will be further integrated into my future work in an attempt to optimize the scientific rigour of my research but also to engage with the internal and external politics of causality, science, and biology in this study.

3) We need to think more critically about using biological evidence for reparative action.

Birth cohort findings on the biology of intergenerational trauma, particularly in the world of behavioral epigenetics, have already made impressionable impacts in community forums,

social institutions, and governments worldwide. Evidence for epigenetic transmission of trauma was considered by The International Criminal Court (ICC) for reparations for war crimes against Hema communities in the DRC (ICC 2017), and the California assembly passed a bill (ACR 177) to "encourage awareness that intergenerational trauma, which has been identified through epigenetic study, may have an impact on the outcomes of certain citizens of California" (Jones-Sawyer 2018). The social applications of this research, however, straddles a fine line between positive social impact and negative bioethical implications.

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We have also seen both implicit and explicit victim blaming of research participants and in particular, vulnerable mothers, who are painted as the scapegoat for poor child health outcomes in a time where maternal exposures to trauma, teratogens, and poor nutrition are seen as a major threat to future child development (Barker et al. 2013; Richardson et al. 2014). Additionally, researchers have warned that the social malleability of hormonal and epigenetic profiles may also introduce a potential "rebiologization" of race (Duster 2015; Meloni 2017). While evidence for transgenerational epigenetic inheritance poses exciting opportunities for ongoing initiatives that aim to hold past oppressive accountable for historical violence, further research must be done before utilizing such information for reparative action.

Nevertheless, emerging research on the biology of intergenerational trauma poses exciting and unprecedented considerations on a wide array of cultural, political, ethical issues globally, and birth cohort studies have become a vital technology through which such biosocial knowledge and debates are being produced. Given the vast, ongoing legacies of structural violence and neocolonialism and the dangerous epistemological authority of "objective" scientific knowledge in public discourse, anthropologists and critical social scientists play a vital role in improving the scientific formation and biosocial impacts of research intergenerational trauma, with the hopes of improving societal well-being and facilitating intergenerational healing.

Bibliography: Chapter 1 (Introduction & Dissertation Overview)

1. Abrahams, N., Mathews, S., Martin, L. J., Lombard, C., & Jewkes, R. (2013). Intimate partner femicide in South Africa in 1999 and 2009. PLoS Med, 10(4), e1001412.
2. Andermahr, S. (2015). "Decolonizing Trauma Studies: Trauma and Postcolonialism"—Introduction. *Humanities*, 500-505.
3. Bhorat, H., & Van der Westhuizen, C. (2010). Poverty, inequality and the nature of economic growth in South Africa. *Testing democracy: Which way is South Africa going*, 46-70.
4. Buss, C., Davis, E. P., Shahbaba, B., Pruessner, J. C., Head, K., & Sandman, C. A. (2012). Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. *Proceedings of the National Academy of Sciences*, 109(20), E1312-E1319.
5. Crais, C. (2011). Poverty, war, and violence in South Africa. Cambridge University Press.
6. Davenport, J. (2013). Digging deep: A history of mining in South Africa. Jonathan Ball Publishers.
7. Drake, A. J., Walker, B. R., & Seckl, J. R. (2005). Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 288(1), R34-R38.
8. Fowler, P. J., Tompsett, C. J., Braciszewski, J. M., Jacques-Tiura, A. J., & Baltes, B. B. (2009). Community violence: A meta-analysis on the effect of exposure and mental health outcomes of children and adolescents. Development and psychopathology, 21(1), 227-259.
9. Glover, V., O'connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. Neuroscience & Biobehavioral Reviews, 35(1), 17-22.
10. Gobodo-Madikizela, P. (Ed.). (2016). Breaking Intergenerational Cycles of Repetition: A Global Dialogue on Historical Trauma and Memory. Opladen; Berlin; Toronto: Verlag Barbara Budrich.
11. Gone, J. P. (2009). A community-based treatment for Native American historical trauma: prospects for evidence-based practice. *Journal of Consulting and Clinical Psychology*, 77(4), 751.
12. Gqola, P. D. (2007). How the 'cult of femininity'and violent masculinities support endemic gender based violence in contemporary South Africa. African Identities, 5(1), 111-124.
13. Gunnar, M. R., DePasquale, C. E., Reid, B. M., & Donzella, B. (2019). Pubertal stress recalibration reverses the effects of early life stress in post-institutionalized children. Proceedings of the National Academy of Sciences, 116(48), 23984-23988.
14. Hickel, J. (2015). Democracy as death: the moral order of anti-liberal politics in South Africa. University of California Press.
15. Hostinar, C. E., & Gunnar, M. R. (2015). Social support can buffer against stress and shape brain activity. *AJOB Neuroscience*, 6(3), 34-42.
16. Kim, A.W. (2020). How should we study intergenerational trauma? Reflections from a 30-year birth cohort study in Soweto, South Africa. *Somatosphere*.

17. Kim, A.W., Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. *Psychological Medicine.*
18. Kim. A.W., Kaiser, B., Bosire, E., Shahbazian, K., Norris, S., Mendenhall E. (2019). Idioms of Resilience among Cancer Patients in Urban South Africa: An Anthropological Heuristic for the Study of Culture and Resilience. *Transcultural Psychiatry.*
19. Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: review and meta-analysis. Schizophrenia research, 161(2-3), 143-149.
20. Lê-Scherban, F., Wang, X., Boyle-Steed, K. H., & Pachter, L. M. (2018). Intergenerational associations of parent adverse childhood experiences and child health outcomes. *Pediatrics*, 141(6).
21. Lin, D., Li, X., Wang, B., Hong, Y., Fang, X., Qin, X., & Stanton, B. (2011). Discrimination, perceived social inequity, and mental health among rural-to-urban migrants in China. Community mental health journal, 47(2), 171-180.
22. Lockhat, R., & Van Niekerk, A. (2000). South African children: A history of adversity, violence and trauma. Ethnicity & Health, 5(3-4), 291-302.
23. Lund, C., De Silva, M., Plagerson, S., Cooper, S., Chisholm, D., Das, J., ... & Patel, V. (2011). Poverty and mental disorders: breaking the cycle in low-income and middle-income countries. The lancet, 378(9801), 1502-1514.
24. Maccari, S., Darnaudery, M., Morley-Fletcher, S., Zuena, A. R., Cinque, C., & Van Reeth, O. (2003). Prenatal stress and long-term consequences: implications of glucocorticoid hormones. *Neuroscience & Biobehavioral Reviews*, 27(1-2), 119-127.
25. Mai, L. G. (2010). An exploration of the intergenerational transmission of historical trauma in Vietnamese Americans. California Institute of Integral Studies.
26. Mandelli, L., Petrelli, C., & Serretti, A. (2015). The role of specific early trauma in adult depression: a meta-analysis of published literature. Childhood trauma and adult depression. European psychiatry, 30(6), 665-680.
27. Mendenhall, E., Kim, A.W. (2019). How to Fail a Scale: Reflections on a Failed Attempt to Assess Resilience. *Culture, Medicine, and Psychiatry.*
28. Mogale, R. S., Burns, K. K., & Richter, S. (2012). Violence against women in South Africa: Policy position and recommendations. Violence against women, 18(5), 580-594.
29. Nowrojee, B. (1995). Violence against women in South Africa: The state response to domestic violence and rape. Human Rights Watch.
30. Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychological bulletin, 129(1), 52.
31. Pieterse, A. L., Todd, N. R., Neville, H. A., & Carter, R. T. (2012). Perceived racism and mental health among Black American adults: A meta-analytic review. Journal of Counseling Psychology, 59(1), 1.
32. PUNAMÄKI, R. L. (1988). Political violence and mental health. International Journal of Mental Health, 17(4), 3-15.

33. Richter, L., Norris, S., Pettifor, J., Yach, D., & Cameron, N. (2007). Cohort profile: Mandela's children: the 1990 Birth to Twenty study in South Africa. International journal of epidemiology, 36(3), 504-511.
34. Schneider, M. L., Roughton, E. C., Koehler, A. J., & Lubach, G. R. (1999). Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. Child development, 70(2), 263-274.
35. Seedat, M., Van Niekerk, A., Jewkes, R., Suffla, S., & Ratele, K. (2009). Violence and injuries in South Africa: prioritising an agenda for prevention. The Lancet, 374(9694), 1011-1022.
36. Smith, A.K., Parets, S.E., Kim, A.W. (2013). Epigenetics of Psychopathology. In Rhee, S.H. & Ronald, A. (Eds.), *Behavior Genetics of Psychopathology*. New York: Springer.
37. Subreenduth, S. (2003). Using a needle to kill an elephant: The politics of race and education in post-apartheid South Africa. Inquiry: Critical thinking across the disciplines, 22(2), 65-73.
38. Thayer, Z.M., Wilson, M.A., Kim, A.W., & Jaeggi, A.V. (2018). Impact of prenatal stress on offspring glucocorticoid levels: A phylogenetic meta-analysis across 14 vertebrate species. Sc*ientific Reports*, 8(1), 4942.
39. Weaver, L. J., & Hadley, C. (2009). Moving beyond hunger and nutrition: a systematic review of the evidence linking food insecurity and mental health in developing countries. Ecology of food and nutrition, 48(4), 263-284.
40. Williams, D. R., Gonzalez, H. M., Williams, S., Mohammed, S. A., Moomal, H., & Stein, D. J. (2008). Perceived discrimination, race and health in South Africa. Social science & medicine, 67(3), 441-452.
41. World Health Organization. (2013). Investing in Mental Health: Evidence for Action. Geneva: World Health Organization.
42. Yehuda, R., Bell, A., Bierer, L. M., & Schmeidler, J. (2008). Maternal, not paternal, PTSD is related to increased risk for PTSD in offspring of Holocaust survivors. *Journal of Psychiatric Research*, 42(13), 1104-1111.

Bibliography: Chapter 2 (Theory)

1) American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.
2) Anda, R. F., Croft, J. B., Felitti, V. J., Nordenberg, D., Giles, W. H., Williamson, D. F., & Giovino, G. A. (1999). Adverse childhood experiences and smoking during adolescence and adulthood. Jama, 282(17), 1652-1658.
3) Arnow, B. A., Blasey, C., Williams, L. M., Palmer, D. M., Rekshan, W., Schatzberg, A. F., ... & Rush, A. J. (2015). Depression subtypes in predicting antidepressant response: a report from the iSPOT-D trial. American Journal of Psychiatry, 172(8), 743-750.
4) Assari, S. (2017). Social determinants of depression: the intersections of race, gender, and socioeconomic status. Brain Sciences, 7(12), 156.
5) Bantjes, J. R., Kagee, A., McGowan, T., & Steel, H. (2016). Symptoms of posttraumatic stress, depression, and anxiety as predictors of suicidal ideation among South African university students. Journal of American college health, 64(6), 429-437.
6) Barbarin, O. A., & Richter, L. M. (2013). Mandela's children: Growing up in post-apartheid South Africa. Routledge.
7) Barker, D. J. (1999). Fetal origins of cardiovascular disease. Annals of medicine, 31(sup1), 3-6.
8) Bauer, G. R. (2014). Incorporating intersectionality theory into population health research methodology: challenges and the potential to advance health equity. Social science & medicine, 110, 10-17.
9) Bebbington, P. E., Brugha, T, MacCarthy, B, Potter, J., Sturt, E.,Wykes, T, Katz, R, & McGuffin, P. (1988). The Camberwell Collabo-rative Depression Study I. Depressed probands: Adversity and theform of depression. British Journal of Psychiatry, 152, 754-765.
10) Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. New England Journal of Medicine, 358(1), 55-68.
11) Belsky, J. (2019). Early-life adversity accelerates child and adolescent development. Current Directions in Psychological Science, 28(3), 241-246.
12) Belujon, P., & Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. International Journal of Neuropsychopharmacology, 20(12), 1036-1046.
13) Berghänel, A., Heistermann, M., Schülke, O., & Ostner, J. (2016). Prenatal stress effects in a wild, long-lived primate: predictive adaptive responses in an unpredictable environment. Proceedings of the Royal Society B: Biological Sciences, 283(1839), 20161304.
14) Bernier, N. J., Bedard, N., & Peter, R. E. (2004). Effects of cortisol on food intake, growth, and forebrain neuropeptide Y and corticotropin-releasing factor gene expression in goldfish. General and comparative endocrinology, 135(2), 230-240.
15) Berry, J. W. (1976). Human ecology and cognitive style: Comparative studies in cultural and psychological adaptation.
16) Berry, J. W. (1997). Immigration, acculturation, and adaptation. Applied psychology, 46(1), 5-34.
17) Betts, K. S., Williams, G. M., Najman, J. M., & Alati, R. (2015). The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioral and emotional problems. Depression and Anxiety, 32(2), 82-90.

18) Blake, K. A. S. (2018). The biology of the fetal period: Interpreting life from fetal skeletal remains. The anthropology of the fetus: Biology, culture, and society, 34-58.
19) Bleuler, M. (1963). Conception of schizophrenia within the last fifty years and today. Proceedings of the Royal Society of Medicine, 56,945-952.
20) Bobo, W. V., Chen, H., Trivedi, M. H., Stewart, J. W., Nierenberg, A. A., Fava, M., ... & Husain, M. M. (2011). Randomized comparison of selective serotonin reuptake inhibitor (escitalopram) monotherapy and antidepressant combination pharmacotherapy for major depressive disorder with melancholic features: a CO-MED report. Journal of affective disorders, 133(3), 467-476.
21) Boku, S., Nakagawa, S., Toda, H., & Hishimoto, A. (2018). Neural basis of major depressive disorder: beyond monoamine hypothesis. Psychiatry and clinical neurosciences, 72(1), 3-12.
22) Bremner, J. D., Southwick, S. M., Johnson, D. R., Yehuda, R., & Charney, D. S. (1993). Childhood physical abuse and combat-related posttraumatic stress disorder in Vietnam veterans. The American journal of psychiatry.
23) Brown, D. E. (1981). General stress in anthropological fieldwork. American Anthropologist, 83(1), 74-92.
24) Buchmann, A.F., Zohsel, K., Blomeyer, D. et al. Interaction between prenatal stress and dopamine D4 receptor genotype in predicting aggression and cortisol levels in young adults. Psychopharmacology 231, 3089–3097 (2014). https://doi.org/10.1007/s00213-014-3484-7
25) Buffa, G., Dahan, S., Sinclair, I., St-Pierre, M., Roofigari, N., Mutran, D., ... & Dancause, K. N. (2018). Prenatal stress and child development: A scoping review of research in low-and middle-income countries. PloS one, 13(12), e0207235.
26) Burns, J. K. (2011). The mental health gap in South Africa: A human rights issue. The Equal Rights Review, 6(99), 99-113.
27) Burns, J. K., & Tomita, A. (2015). Traditional and religious healers in the pathway to care for people with mental disorders in Africa: a systematic review and meta-analysis. Social psychiatry and psychiatric epidemiology, 50(6), 867-877.
28) Buske-Kirschbaum, A., Papousek, M., Pirke, K.-M., Hellhammer, D., & Bolten, M. (2012). Positive life events predict salivary cortisol in pregnant women. Psychoneuroendocrinology, 37(8), 1336–1340. https://doi.org/10.1016/j.psyneuen.2012.01.006
29) Butchart, A., & Emmett, T. (2000). Crime, violence and public health. Behind the Mask. Getting to Grips with Crime and Violence in South Africa. Pretoria, 3-27.
30) Campbell-Hall, V., Petersen, I., Bhana, A., Mjadu, S., Hosegood, V., Flisher, A. J., & MHaPP Research Programme Consortium. (2010). Collaboration between traditional practitioners and primary health care staff in South Africa: developing a workable partnership for community mental health services. Transcultural psychiatry, 47(4), 610-628.
31) Cannon, W. B. (1939). The wisdom of the body. New York WW Norton and Company.
32) Carr, C. P., Martins, C. M. S., Stingel, A. M., Lemgruber, V. B., & Juruena, M. F. (2013). The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. The Journal of nervous and mental disease, 201(12), 1007-1020.
33) Casale, M., Wild, L., Cluver, L., & Kuo, C. (2015). Social support as a protective factor for depression among women caring for children in HIV-endemic South Africa. Journal of behavioral medicine, 38(1), 17-27.

34) Challis JR, Sloboda D, Matthews SG, Holloway A, Alfaidy N, Patel FA, et al. The fetal placental hypothalarnic-pituitary-adrenal (HPA) axis, parturition and post natal health. Mol Cell Endocrinol 2001;185:135-44.
35) Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. Journal of affective disorders, 82(2), 217-225.
36) Chin, E. H., Love, O. P., Verspoor, J. J., Williams, T. D., Rowley, K., & Burness, G. (2009). Juveniles exposed to embryonic corticosterone have enhanced flight performance. Proceedings of the Royal Society of London B: Biological Sciences, 276(1656), 499-505.
37) Cirulli, F., Francia, N., Berry, A., Aloe, L., Alleva, E., & Suomi, S. J. (2009). Early life stress as a risk factor for mental health: role of neurotrophins from rodents to non-human primates. Neuroscience & Biobehavioral Reviews, 33(4), 573-585.
38) Clarke, A. S., Wittwer, D. J., Abbott, D., & Schneider, M. L. (1994). Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys. Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology, 27(5), 257-269.
39) Coe, C. L., Kramer, M., Czéh, B., Gould, E., Reeves, A. J., Kirschbaum, C., & Fuchs, E. (2003). Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. Biological psychiatry, 54(10), 1025-1034.
40) Cohen, S., Kessler, R. C., & Gordon, L. U. (Eds.). (1997). Measuring stress: A guide for health and social scientists. Oxford University Press on Demand.
41) Cole, E. R. (2009). Intersectionality and research in psychology. American psychologist, 64(3), 170.
42) Conching, A. K. S., & Thayer, Z. (2019). Biological pathways for historical trauma to affect health: a conceptual model focusing on epigenetic modifications. Social Science & Medicine, 230, 74-82.
43) Copeland-Linder, N. (2006). Stress among black women in a South African township: The protective role of religion. Journal of Community Psychology, 34(5), 577-599.
44) Coppen, A. (1967). The biochemistry of affective disorders. Br J Psychiatry, 113(504), 1237-1264.
45) Cosci, F., & Chouinard, G. (2019). The Monoamine Hypothesis of Depression Revisited: Could It Mechanistically Novel Antidepressant Strategies?. In Neurobiology of Depression (pp. 63-73). Academic Press.
46) Crenshaw, K. (1989) Demarginalizing the intersection of race and sex: a black feminist critique of antidiscrimination doctrine, feminist theory, and antiracist politics, 1989 University of Chicago Legal Forum, 139.
47) Crenshaw, K. (1990). Mapping the margins: Intersectionality, identity politics, and violence against women of color. Stan. L. Rev., 43, 1241.
48) Cruceanu, C., Matosin, N., & Binder, E. B. (2017). Interactions of early-life stress with the genome and epigenome: from prenatal stress to psychiatric disorders. Current Opinion in Behavioral Sciences, 14, 167-171.
49) Cryan, J. F., O'Riordan, K. J., Cowan, C. S., Sandhu, K. V., Bastiaanssen, T. F., Boehme, M., ... & Guzzetta, K. E. (2019). The microbiota-gut-brain axis. Physiological reviews, 99(4), 1877-2013.

50) Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews neuroscience, 9(1), 46-56.
51) Das-Munshi, J., Lund, C., Mathews, C., Clark, C., Rothon, C., & Stansfeld, S. (2016). Mental health inequalities in adolescents growing up in post-apartheid South Africa: cross-sectional survey, SHaW study. PloS one, 11(5), e0154478.
52) Delgardo, P., & Morena, F. (2006). Neurochemistry of mood disorders. The textbook of mood disorders, 101-116.
53) Denver, R. J. (2009). Structural and functional evolution of vertebrate neuroendocrine stress systems. Trends in Comparative Endocrinology and Neurobiology: Ann. N.Y. Acad. Sci. 1163: 1–16 (2009).
54) Desantis, A. S., Kuzawa, C. W., & Adam, E. K. (2015). Developmental origins of flatter cortisol rhythms: Socioeconomic status and adult cortisol activity. American Journal of Human Biology, 27(4), 458–467. https://doi.org/10.1002/ajhb.22668
55) Dinwiddie, G. Y., Gaskin, D. J., Chan, K. S., Norrington, J., & McCleary, R. (2013). Residential segregation, geographic proximity and type of services used: evidence for racial/ethnic disparities in mental health. Social science & medicine, 80, 67-75.
56) Egbe, C. O., Brooke-Sumner, C., Kathree, T., Selohilwe, O., Thornicroft, G., & Petersen, I. (2014). Psychiatric stigma and discrimination in South Africa: perspectives from key stakeholders. BMC psychiatry, 14(1), 191.
57) Elwell-Sutton, T., Folb, N., Clark, A., Fairall, L. R., Lund, C., & Bachmann, M. O. (2019). Socioeconomic position and depression in South African adults with long-term health conditions: a longitudinal study of causal pathways. Epidemiology and psychiatric sciences, 28(2), 199-209.
58) Evans, C. R. (2019). Modeling the intersectionality of processes in the social production of health inequalities. Social Science & Medicine, 226, 249-253.
59) Fassin, D., & Rechtman, R. (2009). The empire of trauma: An inquiry into the condition of victimhood. Princeton University Press.
60) Fearon, R. P., Tomlinson, M., Kumsta, R., Skeen, S., Murray, L., Cooper, P. J., & Morgan, B. (2017). Poverty, early care and stress reactivity in adolescence: Findings from a prospective, longitudinal study in South Africa. Development and psychopathology, 29(2), 449.
61) Federenko, I. S., Schlotz, W., & Hellhammer, D. H. (2005). Birth weight is associated with salivary cortisol responses to psychosocial stress in adult life. Psychoneuroendocrinology, 30(6), 591–598. https://doi.org/10.1016/j.psyneuen.2005.01.008 "Pluess, M., Wurmser, H.,
62) Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. American journal of preventive medicine, 14(4), 245-258.
63) Fink, G. (Ed.). (2010). Stress science: neuroendocrinology. Academic Press.
64) Francis, D. A. (2019). 'Oh my word; for us African gays it's another story.'Revealing the intersections between race, same sex-sexuality and schooling in South Africa. Race Ethnicity and Education, 1-17.

65) Francis, D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science, 286(5442), 1155-1158.
66) Fride, E., Dan, Y., Feldon, J., Halevy, G., & Weinstock, M. (1986). Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. Physiology & behavior, 37(5), 681-687.
67) Friedrich, M. J. (2017). Depression is the leading cause of disability around the world. Jama, 317(15), 1517-1517.
68) Fulford, A. J., & Harbuz, M. S. (2005). An introduction to the HPA axis. In Techniques in the Behavioral and Neural Sciences (Vol. 15, pp. 43-65). Elsevier.
69) Gass, J. D., Stein, D. J., Williams, D. R., & Seedat, S. (2010). Intimate partner violence, health behaviours, and chronic physical illness among South African women. South African Medical Journal, 100(9), 582-585.
70) Gibbs, A., Dunkle, K., & Jewkes, R. (2018). Emotional and economic intimate partner violence as key drivers of depression and suicidal ideation: A cross-sectional study among young women in informal settlements in South Africa. PloS one, 13(4), e0194885.
71) Giles WB, McLean M, Davies JJ, Smith R. Abnormal umbilical artery Doppler waveforms and cord blood corticotropin-releasing hormone. Obstet Gynecol 1996;87:107-11.
72) Glaser, D. (2000). Child abuse and neglect and the brain—a review. Journal of child psychology and psychiatry, 41(1), 97-116.
73) Glover, V. (2011). Annual research review: prenatal stress and the origins of psychopathology: an evolutionary perspective. Journal of Child Psychology and Psychiatry, 52(4), 356-367.
74) Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. Neuroscience & Biobehavioral Reviews, 35(1), 17-22.
75) Gluckman, P. D., & Hanson, M. A. (2004). The developmental origins of the metabolic syndrome. Trends in Endocrinology & Metabolism, 15(4), 183-187.
76) Gluckman, P. D., Hanson, M. A., & Buklijas, T. (2010). A conceptual framework for the developmental origins of health and disease. Journal of Developmental Origins of Health and Disease, 1(1), 6-18.
77) Goldberg, D. (2011). The heterogeneity of "major depression". World Psychiatry, 10(3), 226.
78) Goldstein, J. M., Hale, T., Foster, S. L., Tobet, S. A., & Handa, R. J. (2019). Sex differences in major depression and comorbidity of cardiometabolic disorders: impact of prenatal stress and immune exposures. Neuropsychopharmacology, 44(1), 59-70.
79) Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A. Y., & Tordjman, S. (2014). Effects of prenatal stress on fetal and child development: a critical literature review. Neuroscience & biobehavioral reviews, 43, 137-162.
80) Häberling, I., Baumgartner, N., Emery, S., Keller, P., Strumberger, M., Nalani, K., ... & Müller-Knapp, U. (2019). Anxious depression as a clinically relevant subtype of pediatric major depressive disorder. Journal of Neural Transmission, 126(9), 1217-1230.
81) Hammen, C. L. (2015). Stress and depression: old questions, new approaches. Current Opinion in Psychology, 4, 80-85.
82) Hartley, M., Tomlinson, M., Greco, E., Comulada, W. S., Stewart, J., Le Roux, I., ... & Rotheram-Borus, M. J. (2011). Depressed mood in pregnancy: prevalence and correlates in two Cape Town peri-urban settlements. Reproductive health, 8(1), 9.

83) Heim, C. M., Entringer, S., & Buss, C. (2019). Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology, 105, 123-137.
84) Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology, 33(6), 693-710.
85) Hijab, E. (2017). Maternal Stress Effects Across Primate and Non-Primate Models (Doctoral dissertation).
86) Hillhouse EW, Grammatopoulos DK. Role of stress peptides during human pregnancy and labour. Reproduction 2002; 124:323-9.
87) Hocoy, D. (1998). Apartheid, racism, and Black mental health in South Africa, and the role of racial identity (Doctoral dissertation, ProQuest Information & Learning).
88) Huizink, A. C., & De Rooij, S. R. (2018). Prenatal stress and models explaining risk for psychopathology revisited: Generic vulnerability and divergent pathways. Development and psychopathology, 30(3), 1041-1062.
89) Janssen, L., Silva Santos, G. L., Muller, H. S., Vieira, A. R. A., de Campos, T. A., & de Paulo Martins, V. (2016). Schistosome-Derived Molecules as Modulating Actors of the Immune System and Promising Candidates to Treat Autoimmune and Inflammatory Diseases. Journal of Immunology Research, 2016.
90) Jesulola, E., Micalos, P., & Baguley, I. J. (2018). Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model-are we there yet?. Behavioural brain research, 341, 79-90.
91) Jewkes, R. K., Dunkle, K., Nduna, M., & Shai, N. (2010). Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. The lancet, 376(9734), 41-48.
92) Joffe, J. M. (1978). Hormonal mediation of the effects of prenatal stress on offspring behavior. In Studies on the Development of Behavior and the Nervous System (Vol. 4, pp. 107-144). Elsevier.
93) Kagee, A. (2010). Psychological distress among persons living with HIV, hypertension, and diabetes. AIDS care, 22(12), 1517-1521.
94) Kagura, J., Adair, L. S., Pisa, P. T., Griffiths, P. L., Pettifor, J. M., & Norris, S. A. (2016). Association of socioeconomic status change between infancy and adolescence, and blood pressure, in South African young adults: Birth to Twenty Cohort. BMJ open, 6(3), e008805.
95) Kaminer, D., & Eagle, G. (2010). Traumatic stress in South Africa. Wits University Press.
96) Kaminer, D., Grimsrud, A., Myer, L., Stein, D. J., & Williams, D. R. (2008). Risk for post-traumatic stress disorder associated with different forms of interpersonal violence in South Africa. Social science & medicine, 67(10), 1589-1595.
97) Kaminer, D., Grimsrud, A., Myer, L., Stein, D. J., & Williams, D. R. (2008). Risk for post-traumatic stress disorder associated with different forms of interpersonal violence in South Africa. Social science & medicine, 67(10), 1589-1595.
98) Karlamangla, A. S., Merkin, S. S., Almeida, D. M., Friedman, E. M., Mogle, J. A., & Seeman, T. E. (2019). Early-life adversity and dysregulation of adult diurnal cortisol rhythm. The Journals of Gerontology: Series B, 74(1), 160-169.
99) Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish National Twin Study of Lifetime Major Depression. Am J Psychiatry 2006;163(1):109–14. [PubMed: 16390897]

100)Kim, A. W., Nyengerai, T., & Mendenhall, E. (2020). Evaluating the mental health impacts of the COVID-19 pandemic: perceived risk of COVID-19 infection and childhood trauma predict adult depressive symptoms in urban South Africa. Psychological Medicine, 1-24.
101)Kirmayer, L. J. (2001). Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. Journal of clinical psychiatry, 62, 22-30.
102)Klasen, S., & Minasyan, A. (2020). Affirmative Action and Intersectionality at the Top: Evidence from South Africa (No. 467). GLO Discussion Paper.
103)Kleinman, A. (1985). Interpreting illness experience and clinical meanings: how I see clinically applied anthropology. Medical Anthropology Quarterly, 16(3), 69-71.
104)Kleinman, A. (2004). Culture and depression. New England Journal of Medicine, 351(10), 951-953.
105)Krontira, A. C., Cruceanu, C., & Binder, E. B. (2020). Glucocorticoids as Mediators of Adverse Outcomes of Prenatal Stress. Trends in Neurosciences.
106)Kuzawa, C. W. (2007). Developmental origins of life history: growth, productivity, and reproduction. American Journal of Human Biology, 19(5), 654-661.
107)Kuzawa, C. W., & Quinn, E. A. (2009). Developmental origins of adult function and health: evolutionary hypotheses. Annual Review of Anthropology, 38, 131-147.
108)Kuzawa, C. W., & Thayer, Z. M. (2011). Timescales of human adaptation: the role of epigenetic processes. Epigenomics, 3(2), 221-234.
109)Lachman, J. M., Cluver, L. D., Boyes, M. E., Kuo, C., & Casale, M. (2014). Positive parenting for positive parents: HIV/AIDS, poverty, caregiver depression, child behavior, and parenting in South Africa. AIDS care, 26(3), 304-313.
110)Lazarus, R. S., & Folkman, S. (1984). Stress, appraisal, and coping. Springer publishing company.
111)Lazarus, R. S., Speisman, J. C., Mordkoff, A. M., & Davison, L. A. (1962). A laboratory study of psychological stress produced by a motion picture film. Psychological Monographs: General and Applied, 76(34), 1.
112)Leonard BE, Song C. 1999. Stress, depression and the role of cytokines. In Cytokines, Stress and Depression, Dantzer R (ed.). Academic Plenum: New York, Kluwer; 251–265.
113)Leonard BE. 2001. Brain cytokines and the psychopathology of depression. In Antidepressants, Leonard BE (ed.). Birkhauser Verlag: Basel; 109– 120.
114)Liu, B., Liu, J., Wang, M., Zhang, Y., & Li, L. (2017). From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. Frontiers in cellular neuroscience, 11, 305.
115)Louw, A. (1997). Surviving the transition: Trends and perceptions of crime in South Africa. Social Indicators Research, 41(1-3), 137-168.
116)Love, O. P., Gilchrist, H. G., Bêty, J., Wynne-Edwards, K. E., Berzins, L., & Williams, T. D. (2009). Using life-histories to predict and interpret variability in yolk hormones. General and comparative endocrinology, 163(1), 169-174.
117)Love, O.P. & Williams, T.D. (2008). The adaptive value of stress-induced phenotypes: effects of maternally derived corticosterone on sex-biased investment, cost of reproduction, and maternal fitness. Am. Nat., 172, E135– E149.
118)Lumsden, D. P. (1981). Is the concept of “stress” of any use, anymore. Contributions to Primary Prevention in Mental Health: Working Papers. Toronto: Canadian Mental Health Association.

119)Lund, C., & Cois, A. (2018). Simultaneous social causation and social drift: Longitudinal analysis of depression and poverty in South Africa. Journal of affective disorders, 229, 396-402.
120)Lund, C., Schneider, M., Garman, E. C., Davies, T., Munodawafa, M., Honikman, S., ... & Joska, J. (2020). Task-sharing of psychological treatment for antenatal depression in Khayelitsha, South Africa: effects on antenatal and postnatal outcomes in an individual randomised controlled trial. Behaviour research and therapy, 130, 103466.
121)Lund, C., Stein, D. J., Corrigall, J., Bradshaw, D., Schneider, M., & Flisher, A. J. (2008). Mental health is integral to public health: a call to scale up evidence-based services and develop mental health research. SAMJ: South African Medical Journal, 98(6), 444-446.
122)Maccari, S., Darnaudery, M., Morley-Fletcher, S., Zuena, A. R., Cinque, C., & Van Reeth, O. (2003). Prenatal stress and long-term consequences: implications of glucocorticoid hormones. Neuroscience & Biobehavioral Reviews, 27(1-2), 119-127.
123)Maccari, S., Piazza, P. V., Kabbaj, M., Barbazanges, A., Simon, H., & Le Moal, M. (1995). Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. Journal of Neuroscience, 15(1), 110-116.
124)Madu, S. N., & Peltzer, K. (2000). Risk factors and child sexual abuse among secondary school students in the Northern Province (South Africa). Child abuse & neglect, 24(2), 259-268.
125)Maletic, V., Eramo, A., Gwin, K., Offord, S. J., & Duffy, R. A. (2017). The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: a systematic review. Frontiers in psychiatry, 8, 42.
126) Manyema, M., Norris, S. A., & Richter, L. M. (2018). Stress begets stress: the association of adverse childhood experiences with psychological distress in the presence of adult life stress. BMC public health, 18(1), 835.
127)Marais, D. L., & Petersen, I. (2015). Health system governance to support integrated mental health care in South Africa: challenges and opportunities. International journal of mental health systems, 9(1), 14.
128)Markham, J. A., & Koenig, J. I. (2011). Prenatal stress: role in psychotic and depressive diseases. Psychopharmacology, 214(1), 89-106.
129)Martinez, A., Israelski, D., Walker, C., & Koopman, C. (2002). Posttraumatic stress disorder in women attending human immunodeficiency virus outpatient clinics. AIDS patient care and STDs, 16(6), 283-291.
130)Martínez, J. A., Cordero, P., Campión, J., & Milagro, F. I. (2012). Interplay of early-life nutritional programming on obesity, inflammation and epigenetic outcomes. Proceedings of the Nutrition Society, 71(2), 276-283.
131)McDade, T. W. (2012). Early environments and the ecology of inflammation. Proceedings of the National Academy of Sciences, 109(Supplement 2), 17281-17288.
132)McGowan, C. J., & Norris, S. A. (2020). Associations of early-life growth with health using an allostatic load score in young, urban African adults: Birth to Twenty Plus Cohort. Journal of developmental origins of health and disease, 11(4), 360-368.
133)McGowan, P. O., & Matthews, S. G. (2018). Prenatal stress, glucocorticoids, and developmental programming of the stress response. Endocrinology, 159(1), 69-82.

134)McIsaac, S. (2020). Identified Patient: Apartheid Syndrome, Political Therapeutics, and Generational Care in South Africa. Medical anthropology quarterly, 34(2), 192-209.
135)McKerracher, L., Fried, R., Kim, A. W., Moffat, T., Sloboda, D. M., & Galloway, T. (2020). Synergies between the Developmental Origins of Health and Disease framework and multiple branches of evolutionary anthropology. Evolutionary Anthropology: Issues, News, and Reviews.
136)McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. Nat Med 1995;1:460-3.
137)Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annual review of neuroscience, 24(1), 1161-1192.
138)Meinck, F., Cluver, L., Loening-Voysey, H., Bray, R., Doubt, J., Casale, M., & Sherr, L. (2017). Disclosure of physical, emotional and sexual child abuse, help-seeking and access to abuse response services in two South African Provinces. Psychology, Health & Medicine, 22(sup1), 94-106.
139)Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Reviews Immunology, 16(1), 22-34.
140)Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychological bulletin, 137(6), 959.
141)Monk, C., Lugo-Candelas, C., & Trumpff, C. (2019). Prenatal developmental origins of future psychopathology: Mechanisms and pathways. Annual review of clinical psychology, 15, 317-344.
142)Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. Psychological Bulletin, 110, 406 – 425.
143)Moodley, J. (2019). The Significance of Intersectionality in Mental Health-Care Policy in South Africa. In The Palgrave Handbook of Intersectionality in Public Policy (pp. 625-640). Palgrave Macmillan, Cham.
144)Moreau, J. (2015). Intersectional citizenship, violence, and lesbian resistance in South Africa. New Political Science, 37(4), 494-508.
145)Muholi, Z. (2004). Thinking through Lesbian Rape. Agenda, 18(61), 118–119.
146)Mulligan, C. J. (2016). Early environments, stress, and the epigenetics of human health. Annual Review of Anthropology, 45, 233-249.
147)Mullings, L. (2014). On our own terms: Race, class, and gender in the lives of African-American Women. Routledge.
148)Mungai, K., & Bayat, A. (2019). An overview of trends in depressive symptoms in South Africa. South African journal of psychology, 49(4), 518-535.
149)Munthali, R. J., Kagura, J., Lombard, Z., & Norris, S. A. (2016). Childhood adiposity trajectories are associated with late adolescent blood pressure: birth to twenty cohort. BMC public health, 16(1), 665.
150)Munthali, R. J., Kagura, J., Lombard, Z., & Norris, S. A. (2017). Early life growth predictors of childhood adiposity trajectories and future risk for obesity: birth to twenty cohort. Childhood Obesity, 13(5), 384-391.

151)Murray, C. M., Stanton, M. A., Wellens, K. R., Santymire, R. M., Heintz, M. R., & Lonsdorf, E. V. (2018). Maternal effects on offspring stress physiology in wild chimpanzees. American journal of primatology, 80(1), e22525.
152)Naidoo, S., Kagura, J., Fabian, J., & Norris, S. A. (2019). Early life factors and longitudinal blood pressure trajectories are associated with elevated blood pressure in early adulthood: BT20 cohort. Hypertension, 73(2), 301-309.
153)Nash, J. C. (2008). Re-thinking intersectionality. Feminist review, 89(1), 1-15.
154)Nemeroff, C. B. (2008). Recent findings in the pathophysiology of depression. Focus, 6(1), 3-14.
155)Nettis, M. A., Pariante, C. M., & Mondelli, V. (2019). Early-life adversity, systemic inflammation and comorbid physical and psychiatric illnesses of adult life. Neuroinflammation and Schizophrenia, 207-225.
156)Ngui, E. M., Khasakhala, L., Ndetei, D., & Roberts, L. W. (2010). Mental disorders, health inequalities and ethics: A global perspective. International Review of Psychiatry, 22(3), 235-244.
157)Ngwepe, P. D. (2017). Relationship between social adversity in two year olds and C-reactive protein in eighteen year olds in the birth-to twenty cohort (Doctoral dissertation).
158)Norris, S. A., Osmond, C., Gigante, D., Kuzawa, C. W., Ramakrishnan, L., Lee, N. R., ... & Fall, C. H. (2012). Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low-or middle-income country birth cohorts. Diabetes care, 35(1), 72-79.
159)Norris, S. A., Roeser, R. W., Richter, L. M., Lewin, N., Ginsburg, C., Fleetwood, S. A., ... & Van Der Wolf, K. (2008). South African-ness among adolescents: The emergence of a collective identity within the birth to twenty cohort study. The Journal of early adolescence, 28(1), 51-69.
160)Núñez Carrasco, L. (2015). Faith healing, migration and gendered conversions in Pentecostal churches in Johannesburg. In Healing and Change in the City of Gold (pp. 149-168). Springer, Cham.
161)Nwakasi, C., Brown, J. S., Subedi, S., & Darlingtina, E. (2020). Depression, functional disability, and accessing health care among older Ghanaians and South Africans: a comparative study based on WHO study on global ageing and adult health (SAGE). Aging & Mental Health, 1-9.
162)Nyirenda, M., Chatterji, S., Rochat, T., Mutevedzi, P., & Newell, M. L. (2013). Prevalence and correlates of depression among HIV-infected and-affected older people in rural South Africa. Journal of affective disorders, 151(1), 31-38.
163)O'Donnell, K. J., & Meaney, M. J. (2017). Fetal origins of mental health: the developmental origins of health and disease hypothesis. American Journal of Psychiatry, 174(4), 319-328.
164)Okada, H., Kuhn, C., Feillet, H., & Bach, J. F. (2010). The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clinical & Experimental Immunology, 160(1), 1-9.
165)Oosterman, M., Schuengel, C., Forrer, M. L., & De Moor, M. H. (2019). The impact of childhood trauma and psychophysiological reactivity on at-risk women's adjustment to parenthood. Development and psychopathology, 31(1), 127-141.
166)Oprea, A., Bonnet, N. C., Pollé, O., & Lysy, P. A. (2019). Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Therapeutic advances in endocrinology and metabolism, 10, 2042018818821294.

167)Palmary, I., Hamber, B., & Núñez, L. (Eds.). (2014). Healing and change in the City of Gold: Case studies of coping and support in Johannesburg (Vol. 24). Springer.
168)Parker, K. J., & Maestripieri, D. (2011). Identifying key features of early stressful experiences that produce stress vulnerability and resilience in primates. Neuroscience & Biobehavioral Reviews, 35(7), 1466-1483.
169)Patel, V., & Prince, M. (2010). Global mental health: a new global health field comes of age. Jama, 303(19), 1976-1977.
170)Paykel, E. S. (1976). Life stress, depression and attempted suicide. Journal of Human Stress, 2(3), 3-12.
171)Peltzer, K., & Pengpid, S. (2020). Social determinants of depression among adults in South Africa. Journal of Human Behavior in the Social Environment, 1-8.
172)Peltzer, K., Pengpid, S., McFarlane, J., & Banyini, M. (2013). Mental health consequences of intimate partner violence in Vhembe district, South Africa. General Hospital Psychiatry, 35(5), 545-550.
173)Petersen, I., Bhana, A., Baillie, K., & MhaPP Research Programme Consortium. (2012a). The feasibility of adapted group-based interpersonal therapy (IPT) for the treatment of depression by community health workers within the context of task shifting in South Africa. Community mental health journal, 48(3), 336-341.
174)Petersen, I., Hancock, J. H., Bhana, A., & Govender, K. (2014). A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: a randomized controlled pilot study. Journal of affective disorders, 158, 78-84.
175)Petersen, I., Lund, C., Bhana, A., Flisher, A. J., & Mental Health and Poverty Research Programme Consortium. (2012b). A task shifting approach to primary mental health care for adults in South Africa: human resource requirements and costs for rural settings. Health policy and planning, 27(1), 42-51.
176)Pine, D. S., Cohen, E., Cohen, P., & Brook, J. (1999). Adolescent depressive symptoms as predictors of adult depression: moodiness or mood disorder?. American Journal of Psychiatry, 156(1), 133-135.
177)Pine, D. S., Cohen, P., Brook, J., Gurley, D., & Ma, Y. (1998). Anxiety and depression in adolescence as predictors of anxiety and depression in adulthood. Archives of General Psychiatry, 55, 56-66.
178)Pine, D. S., Cohen, P., Johnson, J. G., & Brook, J. S. (2002). Adolescent life events as predictors of adult depression. Journal of affective disorders, 68(1), 49-57.
179)Ping, E. Y., Laplante, D. P., Elgbeili, G., Jones, S. L., Brunet, A., & King, S. (2020). Disaster-related prenatal maternal stress predicts HPA reactivity and psychopathology in adolescent offspring: Project Ice Storm. Psychoneuroendocrinology, 104697.
180)Raison, C. L. & Miller, A. H. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol. Psychiatry 18, 15–37 (2013).
181)Raleva, M. (2018). Early life stress: a key link between childhood adversity and risk of attempting suicide. Psychiatr Danub, 30(Suppl 6), 341-347.
182)Ramanan, D., Bowcutt, R., Lee, S. C., San Tang, M., Kurtz, Z. D., Ding, Y., & Lim, Y. A. (2016). Helminth infection promotes colonization resistance via type 2 immunity. Science, 352(6285), 608-612.
183)Ramirez-Avila, L., Regan, S., Giddy, J., Chetty, S., Ross, D., Katz, J. N., ... & Bassett, I. V. (2012). Depressive symptoms and their impact on health-seeking behaviors in newly-

diagnosed HIV-infected patients in Durban, South Africa. AIDS and Behavior, 16(8), 2226-2235.
184)Ramkisson, S., Pillay, B. J., & Sartorius, B. (2016). Anxiety, depression and psychological well-being in a cohort of South African adults with Type 2 diabetes mellitus. South African Journal of Psychiatry, 22(1).
185)Remien, R. H., Stirratt, M. J., Nguyen, N., Robbins, R. N., Pala, A. N., & Mellins, C. A. (2019). Mental health and HIV/AIDS: the need for an integrated response. AIDS (London, England), 33(9), 1411.
186)Richter, L. M., Mathews, S., Kagura, J., & Nonterah, E. (2018). A longitudinal perspective on violence in the lives of South African children from the Birth to Twenty Plus cohort study in Johannesburg-Soweto. South African Medical Journal, 108(3), 181-186.
187)Rivera-Rivera, Y., Vázquez-Santiago, F. J., Albino, E., Sánchez, M. D. C., & Rivera-Amill, V. (2016). Impact of depression and inflammation on the progression of HIV disease. Journal of clinical & cellular immunology, 7(3).
188)Robins, C. J., & Block, P. (1989). Cognitive theories of depression viewed from a diathesis-stress perspective: Evaluations of the models of Beck and of Abramson, Seligman, and Teasdale. Cognitive Therapy and Research, 13, 297-313.
189)Robinson, B. G., Emanuel, R. L., Frim, D. M., & Majzoub, J. A. (1988). Glucocorticoid stimulates expression of corticotropin-releasing hormone gene in human placenta. Proceedings of the National Academy of Sciences, 85(14), 5244-5248.
190)Rochat, T. J., Richter, L. M., Doll, H. A., Buthelezi, N. P., Tomkins, A., & Stein, A. (2006). Depression among pregnant rural South African women undergoing HIV testing. Jama, 295(12), 1373-1378.
191)Rook, G. A., & Lowry, C. A. (2008). The hygiene hypothesis and psychiatric disorders. Trends in immunology, 29(4), 150-158.
192)Rosenbaum, S., Zeng, S., Campos, F. A., Gesquiere, L. R., Altmann, J., Alberts, S. C., ... & Archie, E. A. (2020). Social bonds do not mediate the relationship between early adversity and adult glucocorticoids in wild baboons. Proceedings of the National Academy of Sciences, 117(33), 20052-20062.
193)Rosenthal, D. (1963). A suggested conceptual framework. In D. Rosenthal (Ed.), The Genain quadruplets (505-516). New York: Basic Books.
194)Round, J. L., O'Connell, R. M. & Mazmanian, S. K. Coordination of tolerogenic immune responses by the commensal microbiota. J. Autoimmun. 34, J220–J225 (2010).
195)Sabet, F., Richter, L. M., Ramchandani, P. G., Stein, A., Quigley, M. A., & Norris, S. A. (2009). Low birthweight and subsequent emotional and behavioural outcomes in 12-year-old children in Soweto, South Africa: findings from Birth to Twenty. International journal of epidemiology, 38(4), 944-954.
196)Said-Mohamed, R., Stein, A. D., Pettifor, J. M., & Norris, S. A. (2019). Sanitation and diarrhoea in infancy and CRP level at 18 years: the birth-to-twenty plus cohort. Annals of Human Biology, 46(5), 415-424.
197)Said-Mohamed, R., Pettifor, J. M., & Norris, S. A. (2018). Life History theory hypotheses on child growth: Potential implications for short and long-term child growth, development and health. American journal of physical anthropology, 165(1), 4-19.

198)Sánchez, M. M., Noble, P. M., Lyon, C. K., Plotsky, P. M., Davis, M., Nemeroff, C. B., & Winslow, J. T. (2005). Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. Biological psychiatry, 57(4), 373-381.
199)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.
200)Schülke, O., Ostner, J., & Berghänel, A. (2019). Prenatal maternal stress effects on the development of primate social behavior. Behavioral Ecology and Sociobiology, 73(9), 128.
201)Schulz, A. J., & Mullings, L. E. (2006). Gender, race, class, & health: Intersectional approaches. Jossey-Bass.
202)Seedat, S., Stein, D. J., Jackson, P. B., Heeringa, S. G., Williams, D. R., & Myer, L. (2009). Life stress and mental disorders in the South African stress and health study. South African Medical Journal, 99(5).
203)Seedat, S., Stein, D. J., Jackson, P. B., Heeringa, S. G., Williams, D. R., & Myer, L. (2009). Life stress and mental disorders in the South African stress and health study. South African Medical Journal, 99(5).
204)Seedat, S., Stein, M. B., Kennedy, C. M., & Hauger, R. L. (2003). Plasma cortisol and neuropeptide Y in female victims of intimate partner violence. Psychoneuroendocrinology, 28(6), 796-808.
205)Selye, H. (1946). The general adaptation syndrome and the diseases of adaptation. The journal of clinical endocrinology, 6(2), 117-230.
206)Sheriff, M. J., & Love, O. P. (2013). Determining the adaptive potential of maternal stress. Ecology letters, 16(2), 271-280.
207)Sheriff, M.J., Krebs, C.J. & Boonstra, R. (2009). The sensitive hare: sublethal effects of predator stress on reproduction in snowshoe hares. J. Anim. Ecol., 78, 1249–1258.
208)Shyn SI, Hamilton SP. The Genetics of Major Depression: Moving Beyond the Monoamine Hypothesis. Psychiatr Clin North Am 2010;33(1):125–40.
209)Simbayi, L. C., Kalichman, S., Strebel, A., Cloete, A., Henda, N., & Mqeketo, A. (2007). Internalized stigma, discrimination, and depression among men and women living with HIV/AIDS in Cape Town, South Africa. Social science & medicine, 64(9), 1823-1831.
210)Smith R, Mesiano S, Chan EC, Brown S, Jaffe RB. Corticotropinreleasing hormone directly and preferentially stimulates dehydroepiandrosterone sulfate secretion in fetal adrenal cortical cells. J Clin Endocrinol Metab 1998;83:2916-20.
211)Smith R, Mesiano S, McGrath S. Hormone trajectories leading to human birth. Regul Pept 2002;108:159-64
212)Somhlaba, N. Z., & Wait, J. W. (2009). Stress, coping styles, and spousal bereavement: exploring patterns of grieving among black widowed spouses in rural South Africa. Journal of Loss and Trauma, 14(3), 196-210.
213)Sorsdahl, K., Stein, D. J., Grimsrud, A., Seedat, S., Flisher, A. J., Williams, D. R., & Myer, L. (2009). Traditional healers in the treatment of common mental disorders in South Africa. The Journal of nervous and mental disease, 197(6), 434.
214)Spies, G., Konkiewitz, E. C., & Seedat, S. (2018). Incidence and persistence of depression among women living with and without HIV in South Africa: a longitudinal study. AIDS and Behavior, 22(10), 3155-3165.

215)Spies, G., Konkiewitz, E. C., & Seedat, S. (2018). Incidence and persistence of depression among women living with and without HIV in South Africa: a longitudinal study. AIDS and Behavior, 22(10), 3155-3165.
216)Stenzel-Poore, M. P., Heldwein, K. A., Stenzel, P., Lee, S., & Vale, W. W. (1992). Characterization of the genomic corticotropin-releasing factor (CRF) gene from Xenopus laevis: two members of the CRF family exist in amphibians. Molecular Endocrinology, 6(10), 1716-1724.
217)Strawbridge, R., Young, A. H., & Cleare, A. J. (2017). Biomarkers for depression: recent insights, current challenges and future prospects. Neuropsychiatric disease and treatment.
218)Stroud, L. R., Papandonatos, G. D., Parade, S. H., Salisbury, A. L., Phipps, M. G., Lester, B., ... & Marsit, C. J. (2016). Prenatal major depressive disorder, placenta glucocorticoid and serotonergic signaling, and infant cortisol response. Psychosomatic medicine, 78(9), 979.
219)Strumpher, J., Van Rooyen, R. M., Topper, K., Andersson, L. M. C., & Schierenback, I. (2014). Barriers to accessing mental health care in the Eastern Cape Province of South Africa. Africa Journal of Nursing and Midwifery, 16(1), 45-59.
220)The South African Depression and Anxiety Group. (2020). What is a Depression Disorder? http://www.sadag.org/index.php?option=com_content&view=article&id=9&Itemid=112
221)Tomita, A., Ramlall, S., Naidu, T., Mthembu, S. S., Padayatchi, N., & Burns, J. K. (2019). Major depression and household food insecurity among individuals with multidrug-resistant tuberculosis (MDR-TB) in South Africa. Social psychiatry and psychiatric epidemiology, 54(3), 387-393.
222)Tomita, A., Vandormael, A. M., Cuadros, D., Slotow, R., Tanser, F., & Burns, J. K. (2017). Proximity to healthcare clinic and depression risk in South Africa: geospatial evidence from a nationally representative longitudinal study. Social psychiatry and psychiatric epidemiology, 52(8), 1023-1030.
223)Tomlinson, M., Grimsrud, A. T., Stein, D. J., Williams, D. R., & Myer, L. (2009). The epidemiology of major depression in South Africa: results from the South African stress and health study. South African Medical Journal, 99(5).
224)Tomlinson, M., Grimsrud, A. T., Stein, D. J., Williams, D. R., & Myer, L. (2009). The epidemiology of major depression in South Africa: results from the South African stress and health study. South African Medical Journal, 99(5).
225)Turbeville, A., Aber, J. L., Weinberg, S. L., Richter, L., & van Heerden, A. (2019). The relationship between multidimensional economic well-being and children's mental health, physical health, and executive function development in South Africa. Developmental science, 22(5), e12846.
226)Turner, R. J., & Lloyd, D. A. (1995). Lifetime traumas and mental health: The significance of cumulative adversity. Journal of health and social behavior, 360-376.
227)Van der Kolk, B. A. (2003). Psychological trauma. American Psychiatric Pub.
228)Van Niekerk, A., Suffla, S., & Seedat, M. (2012). Crime, violence and injury in South Africa: 21st century solutions for child safety. Johannesburg: Psychological Society of South Africa.
229)Vearey, J., & Nunez, L. (2010). Migration and Health in South Africa–A review of the current situation and recommendations for achieving the World Health Assembly Resolution on the Health of Migrants. Pretoria, South Africa.

230)Vineis, P., Avendano-Pabon, M., Barros, H., Bartley, M., Carmeli, C., Carra, L., ... & Fraga, S. (2020). Special Report: The Biology of Inequalities in Health: The Lifepath Consortium. Frontiers in Public Health, 8.
231)Viruell-Fuentes, E. A., Miranda, P. Y., & Abdulrahim, S. (2012). More than culture: structural racism, intersectionality theory, and immigrant health. Social science & medicine, 75(12), 2099-2106.
232)Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA. Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. Psychosom Med 1996;58: 432-6.
233)Wadhwa PD, Sandman CA, Chicz-DeMet A, Porto M. Placental CRH modulates maternal pituitary adrenal function in human pregnancy. Ann N Y Acad Sci 1997;814:276-81.
234)Wadhwa, P. D. (2005). Psychoneuroendocrine processes in human pregnancy influence fetal development and health. Psychoneuroendocrinology, 30(8), 724-743.
235)Wadhwa, P. D., Garite, T. J., Porto, M., Glynn, L., Chicz-DeMet, A., Dunkel-Schetter, C., & Sandman, C. A. (2004). Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. American journal of obstetrics and gynecology, 191(4), 1063-1069.
236)Wan, L., Li, Y., Zhang, Z., Sun, Z., He, Y., & Li, R. (2018). Methylenetetrahydrofolate reductase and psychiatric diseases. Translational psychiatry, 8(1), 1-12.
237)Watamura, S. E., & Roth, T. L. (2019). Looking back and moving forward: evaluating and advancing translation from animal models to human studies of early life stress and DNA methylation. Developmental psychobiology, 61(3), 323-340.
238)Watters, E. (2010). Crazy like us: The globalization of the American psyche. Simon and Schuster.
239)Weinstock, M. (2008). The long-term behavioural consequences of prenatal stress. Neuroscience & Biobehavioral Reviews, 32(6), 1073-1086.
240)Welberg, L. A., & Seckl, J. R. (2001). Prenatal stress, glucocorticoids and the programming of the brain. Journal of neuroendocrinology, 13(2), 113-128.
241)Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., ... & Burstein, R. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. The lancet, 382(9904), 1575-1586.
242)Williams, D. R., Gonzalez, H. M., Williams, S., Mohammed, S. A., Moomal, H., & Stein, D. J. (2008). Perceived discrimination, race and health in South Africa. Social science & medicine, 67(3), 441-452.
243)Williams, D. R., Gonzalez, H. M., Williams, S., Mohammed, S. A., Moomal, H., & Stein, D. J. (2008). Perceived discrimination, race and health in South Africa. Social science & medicine, 67(3), 441-452.
244)Williams, S. L., Williams, D. R., Stein, D. J., Seedat, S., Jackson, P. B., & Moomal, H. (2007). Multiple traumatic events and psychological distress: the South Africa stress and health study. Journal of traumatic stress, 20(5), 845-855.
245)Womersley, J. S., Martin, L. I., van der Merwe, L., Seedat, S., & Hemmings, S. M. (2018). Hypothalamic-pituitary-adrenal axis variants and childhood trauma influence anxiety sensitivity in South African adolescents. Metabolic Brain Disease, 33(2), 601-613.

246)Womersley, J. S., Seedat, S., & Hemmings, S. M. (2017). Childhood maltreatment and HIV-associated neurocognitive disorders share similar pathophysiology: a potential sensitisation mechanism?. Metabolic brain disease, 32(5), 1717-1733.
247)Wong, F. Y., Huang, Z. J., DiGangi, J. A., Thompson, E. E., & Smith, B. D. (2008). Gender differences in intimate partner violence on substance abuse, sexual risks, and depression among a sample of South Africans in Cape Town, South Africa. AIDS Education and Prevention, 20(1), 56-64.
248)World Bank. (2020). New country classifications by income level: 2019-2020. Accessed on 21 September 2020: https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2019-2020
249)World Health Organization, & UNICEF. (2019). WHO low birthweight estimates: levels and trends 2000–2015. No. WHO/NMH/NHD/19.21. United Nations Children's Fund (UNICEF).
250)Wray, N. R., & Gottesman, I. I. (2012). Using summary data from the danish national registers to estimate heritabilities for schizophrenia, bipolar disorder, and major depressive disorder. Frontiers in genetics, 3, 118.
251)Yang, S. J., Stewart, R., Kang, H. J., Kim, S. Y., Bae, K. Y., Kim, J. M., ... & Jun, T. Y. (2013). Response to antidepressants in major depressive disorder with melancholic features: the CRESCEND study. Journal of affective disorders, 144(1-2), 42-50.
252)Yang, Y., Yang, D., Tang, G., Zhou, C., Cheng, K., Zhou, J., ... & Chen, J. (2013). Proteomics reveals energy and glutathione metabolic dysregulation in the prefrontal cortex of a rat model of depression. Neuroscience, 247, 191-200.
253)Zuckerman, M. (1999). Vulnerability to psychopathology: A biosocial model. Washington, DC: American Psychological Association.

Bibliography: Chapter 3 (Methods)

1. Adair, L. S., Popkin, B. M., Akin, J. S., Guilkey, D. K., Gultiano, S., Borja, J., ... & Hindin, M. J. (2011). Cohort profile: the Cebu longitudinal health and nutrition survey. International journal of epidemiology, 40(3), 619-625.
2. Adam, E. K., & Kumari, M. (2009). Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology, 34(10), 1423-1436.
3. Alexander, P., Ceruti, C., Motseke, K., Phadi, M., & Wale, K. (2013). Class in Soweto. University of KwaZulu-Natal Press.
4. Barnard, A. (2008). Ethnographic analogy and the reconstruction of early Khoekhoe society. Southern African Humanities, 20(1), 61-75.
5. Bonner, P. L., & Segal, L. (1998). Soweto: A history. Maskew Miller Longman.
6. Britannica. (2020). South Africa. https://www.britannica.com/place/South-Africa
7. Crais, C., & McClendon, T. V. (Eds.). (2013). The South Africa reader: history, culture, politics. Duke University Press.
8. Harrison, D. (1983). The white tribe of Africa (Vol. 31). Univ of California Press.
9. McKendrick, B., & Hoffmann, W. (Eds.). (1990). People and violence in South Africa. Oxford University Press, USA.
10. Melamed, Jodi. (2015). "Racial Capitalism". Critical Ethnic Studies. 1 (1): 76–85.
11. Ndlovu, S. M. (2006). The Soweto Uprising. The road to democracy in South Africa, 2, 1970-1980.
12. Norris, S. A., Richter, L. M., & Fleetwood, S. A. (2007). Panel studies in developing countries: case analysis of sample attrition over the past 16 years within the birth to twenty cohort in Johannesburg, South Africa. Journal of International Development: The Journal of the Development Studies Association, 19(8), 1143-1150.
13. Paris, J. C., & Gallin, B. (1977). AAA Boycott of South Africa Called for. Anthropology News, 18(1), 2-2.
14. Radin, J., & Cameron, N. (2012). Studying Mandela's Children: Human Biology in Post-Apartheid South Africa: An Interview with Noel Cameron. Current Anthropology, 53(S5), S256-S266.
15. Richter, L. M., Victora, C. G., Hallal, P. C., Adair, L. S., Bhargava, S. K., Fall, C. H., ... & Stein, A. D. (2012). Cohort profile: the consortium of health-orientated research in transitioning societies. International journal of epidemiology, 41(3), 621-626.
16. Robinson, C. J. (2000). Black Marxism: The making of the Black radical tradition. Univ of North Carolina Press.
17. Seekings, J., & Nattrass, N. (2008). Class, race, and inequality in South Africa. Yale University Press.
18. South African History Online. (2020). The South African general elections: 1994. https://www.sahistory.org.za/article/south-african-general-elections-1994.
19. Welsh, D. (2010). The rise and fall of apartheid: From racial domination to majority rule. Jonathan ball publishers.

Bibliography: Chapter 4 (S1000)

1. Abel, E. L. (1980). Smoking during pregnancy: a review of effects on growth and development of offspring. Human biology, 593-625.
2. Ae-Ngibise, K., Jack, D., Wylie, B., Oppong, F., Kaali, S., Agyei, O., Kinney, P., Wright, R., Asante, K., Lee, A. and GRAPHS study team. (2019). Impact of prenatal maternal stress on birth anthropometrics and pregnancy outcomes in rural Ghana. Environmental Epidemiology, 3, 4.
3. Alexander, P., Ceruti, C., Motseke, K., Phadi, M., & Wale, K. (2013). Class in Soweto. University of KwaZulu-Natal Press.
4. Barker, D. J. (1998). In utero programming of chronic disease. Clinical science, 95(2), 115-128.
5. Beijers, R., Buitelaar, J. K., & de Weerth, C. (2014). Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. European child & adolescent psychiatry, 23(10), 943-956.
6. Berghänel, A., Heistermann, M., Schülke, O., & Ostner, J. (2017). Prenatal stress accelerates offspring growth to compensate for reduced maternal investment across mammals. Proceedings of the National Academy of Sciences, 114(50), E10658-E10666.
7. Berkowitz, G. S., Wolff, M. S., Janevic, T. M., Holzman, I. R., Yehuda, R., & Landrigan, P. J. (2003). The World Trade Center disaster and intrauterine growth restriction. Jama, 290(5), 595-596.
8. Bradshaw, D., Bourne, D., & Nannan, N. (2003). What are the leading causes of death among South African children. MRC policy brief, 3, 1-4.
9. Bolten, M. I., Wurmser, H., Buske-Kirschbaum, A., Papoušek, M., Pirke, K. M., & Hellhammer, D. (2011). Cortisol levels in pregnancy as a psychobiological predictor for birthweight. Archives of women's mental health, 14(1), 33-41.
10. Bussieres, E. L., Tarabulsy, G. M., Pearson, J., Tessier, R., Forest, J. C., & Giguere, Y. (2015). Maternal prenatal stress and infant birthweight and gestational age: A meta-analysis of prospective studies. Developmental Review, 36, 179-199.
11. Class, Q. A., Lichtenstein, P., Långström, N., & D'onofrio, B. M. (2011). Timing of prenatal maternal exposure to severe life events and adverse pregnancy outcomes: a population study of 2.6 million pregnancies. Psychosomatic medicine, 73(3), 234.
12. Collins J. W., David, R. J., Handler, A., Wall, S., & Andes, S. (2004). Very low birthweight in African American infants: the role of maternal exposure to interpersonal racial discrimination. American journal of public health, 94(12), 2132-2138.
13. Coussons-Read, M. E., Lobel, M., Carey, J. C., Kreither, M. O., D'Anna, K., Argys, L., Ross, R.G., Brandt, C. & Cole, S. (2012). The occurrence of preterm delivery is linked to pregnancy- specific distress and elevated inflammatory markers across gestation. Brain, behavior, and immunity, 26(4), 650-659.
14. Cox, J. L., Chapman, G., Murray, D., & Jones, P. (1996). Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. Journal of affective disorders, 39(3), 185-189.
15. D'Anna-Hernandez, K. L., Hoffman, M. C., Zerbe, G. O., Coussons-Read, M., Ross, R. G., & Laudenslager, M. L. (2012). Acculturation, maternal cortisol and birth outcomes in women of Mexican descent. Psychosomatic Medicine, 74(3), 296.

16. Diego, M.A., Field, T., Hernandez-Reif, M., Schanberg, S., Kuhn, C., Gonzalez-Quintero, V.H., 2009. Prenatal depression restricts fetal growth. Early Human Development. 85, 65-70. Doi:10.1016/j.earlhumdev.2008.07.002.
17. Ding, X.X., Wu, Y.L., Xu, S.J., Zhu, R.P., Jia, X.M., Zhang, S.F., Huang, K., Zhu, P., Hao, J.H., & Tao, F.B. (2014). Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. Journal of affective disorders, 159, 103-110.
18. Engel, S. M., Berkowitz, G. S., Wolff, M. S., & Yehuda, R. (2005). Psychological trauma associated with the World Trade Center attacks and its effect on pregnancy outcome. Paediatric and perinatal epidemiology, 19(5), 334-341.
19. Field, T., & Diego, M. (2008). Cortisol: the culprit prenatal stress variable. International Journal of Neuroscience, 118(8), 1181-1205.
20. Field, T., Diego, M., & Hernandez-Reif, M. (2006). Prenatal depression effects on the fetus and newborn: a review. Infant Behavior and Development, 29(3), 445-455.
21. Gitau, R., Fisk, N. M., & Glover, V. (2001). Maternal stress in pregnancy and its effect on the human foetus: an overview of research findings. Stress, 4(3), 195-203.
22. Glover, V., Bergman, K., Sarkar, P., & O'Connor, T. G. (2009). Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. Psychoneuroendocrinology, 34(3), 430-435.
23. Glover, V., & O'Connor, T. G. (2002). Effects of antenatal stress and anxiety: implications for development and psychiatry. The British Journal of Psychiatry, 180(5), 389-391.
24. Glynn, L. M., Wadhwa, P. D., Dunkel-Schetter, C., Chicz-DeMet, A., & Sandman, C. A. (2001). When stress happens matters: effects of earthquake timing on stress responsivity in pregnancy. American journal of obstetrics and gynecology, 184(4), 637-642.
25. Glynn, L. M., Schetter, C. D., Hobel, C. J., & Sandman, C. A. (2008). Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. Health Psychology, 27(1), 43.
26. Goedhart, G., Vrijkotte, T. G., Roseboom, T. J., van der Wal, M. F., Cuijpers, P., & Bonsel, G. J. (2010). Maternal cortisol and offspring birthweight: results from a large prospective cohort study. Psychoneuroendocrinology, 35(5), 644-652.
27. Grote, N. K., Bridge, J. A., Gavin, A. R., Melville, J. L., Iyengar, S., & Katon, W. J. (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birthweight, and intrauterine growth restriction. Archives of general psychiatry, 67(10), 1012-1024.
28. Harder, T., Rodekamp, E., Schellong, K., Dudenhausen, J. W., & Plagemann, A. (2007). Birthweight and subsequent risk of type 2 diabetes: a meta-analysis. American journal of epidemiology, 165(8), 849-857.
29. Hobel, C. J., Goldstein, A. M. Y., & Barrett, E. S. (2008). Psychosocial stress and pregnancy outcome. Clinical obstetrics and gynecology, 51(2), 333-348.
30. Jones, A., Godfrey, K. M., Wood, P., Osmond, C., Goulden, P., & Phillips, D. I. (2006). Fetal growth and the adrenocortical response to psychological stress. The Journal of Clinical Endocrinology & Metabolism, 91(5), 1868-1871.
31. Khashan, A. S., Everard, C., McCowan, L. M. E., Dekker, G., Moss-Morris, R., Baker, P. N., et al. (2014). Second-trimester maternal distress increases the risk of small for gestational age. Psychological Medicine, 44, 1–12.

32. Khashan, A. S., McNamee, R., Abel, K. M., Pedersen, M. G., Webb, R. T., Kenny, L. C., et al. (2008). Reduced infant birthweight consequent upon maternal exposure to severe life events. Psychosomatic Medicine, 70, 688–694.
33. Kramer MS. 1987. Determinants of low birthweight: methodological assessment and meta-analysis. Bull WHO 65:663–737.
34. Kuzawa, C. W., & Sweet, E. (2009). Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. American Journal of Human Biology: The Official Journal of the Human Biology Association, 21(1), 2-15.
35. Lederman, S. A., Rauh, V., Weiss, L., Stein, J. L., Hoepner, L. A., Becker, M., & Perera, F. P. (2004). The effects of the World Trade Center event on birth outcomes among term deliveries at three lower Manhattan hospitals. Environmental health perspectives, 112(17), 1772-1778.
36. Lee, B. J., & Lim, S. H. (2010). Risk of low birthweight associated with family poverty in Korea. Children and Youth Services Review, 32(12), 1670-1674.
37. Levitt, N. S., Lambert, E. V., Woods, D., Hales, C. N., Andrew, R., & Seckl, J. R. (2000). Impaired glucose tolerance and elevated blood pressure in low birthweight, nonobese, young South African adults: early programming of cortisol axis. The Journal of Clinical Endocrinology & Metabolism, 85(12), 4611-4618.
38. Lobel, M., Cannella, D. L., Graham, J. E., DeVincent, C., Schneider, J., & Meyer, B. A. (2008). Pregnancy-specific stress, prenatal health behaviors, and birth outcomes. Health Psychology, 27, 604–615.
39. Magee, B. D., Hattis, D., & Kivel, N. M. (2004). Role of smoking in low birthweight. The Journal of reproductive medicine, 49(1), 23-27.
40. Marteau, T. M., & Bekker, H. (1992). The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). British journal of clinical Psychology, 31(3), 301-306.
41. Mattison D, Damus K, Fiore E, Petrini J, Alter C. 2001. Preterm delivery: a public health perspective. Pediat Perinat Epidemiol 15:7–16.
42. Majzoub, J. A., & Karalis, K. P. (1999). Placental corticotropin-releasing hormone: function and regulation. American journal of obstetrics and gynecology, 180(1), S242-S246.
43. McDade, T. W., Rutherford, J., Adair, L., & Kuzawa, C. W. (2009). Early origins of inflammation: microbial exposures in infancy predict lower levels of C-reactive protein in adulthood. Proceedings of the Royal Society B: Biological Sciences, 277(1684), 1129-1137.
44. Mu, M., Wang, S. F., Sheng, J., Zhao, Y., Li, H. Z., Hu, C. L., & Tao, F. B. (2012). Birthweight and subsequent blood pressure: a meta-analysis. Archives of cardiovascular diseases, 105(2), 99-113.
45. Murphy, V. E., & Clifton, V. L. (2003). Alterations in human placental 11β-hydroxysteroid dehydrogenase type 1 and 2 with gestational age and labour. Placenta, 24(7), 739-744.
46. Obel, C., Hedegaard, M., Henriksen, T. B., Secher, N. J., Olsen, J., & Levine, S. (2005). Stress and salivary cortisol during pregnancy. Psychoneuroendocrinology, 30(7), 647-656.
47. O'Donnell, K., O'Connor, T. G., & Glover, V. (2009). Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Developmental neuroscience, 31(4), 285-292.

48. O'Donnell, K. J., Jensen, A. B., 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.
49. Pagel, M. D., Smilkstein, G., Regen, H., & Montano, D. (1990). Psychosocial influences on new born outcomes: a controlled prospective study. Social science & medicine, 30(5), 597-604.
50. Patil, D., Enquobahrie, D. A., Peckham, T., Seixas, N., & Hajat, A. (2020). Retrospective cohort study of the association between maternal employment precarity and infant low birth weight in women in the USA. BMJ open, 10(1).
51. Quigley, M. E., Sheehan, K. L., Wilkes, M. M., & Yen, S. S. C. (1979). Effects of maternal smoking on circulating catecholamine levels and fetal heart rates. American Journal of Obstetrics and Gynecology, 133(6), 685-690.
52. Ramchandani, P. G., Richter, L. M., Norris, S. A., & Stein, A. (2010). Maternal prenatal stress and later child behavioral problems in an urban South African setting. Journal of the American Academy of Child & Adolescent Psychiatry, 49(3), 239-247.
53. Resnik, R. (2002). Intrauterine growth restriction. Obstetrics & Gynecology, 99(3), 490-496.
54. Rondó, P. H., Ferreira, R. F., Nogueira, F., Ribeiro, M. C., Lobert, H., & Artes, R. (2003). Maternal psychological stress and distress as predictors of low birthweight, prematurity and intrauterine growth retardation. European journal of clinical nutrition, 57(2), 266.
55. Rosa, M. J., Nentin, F., Bosquet Enlow, M., Hacker, M. R., Pollas, N., Coull, B., & Wright, R. J. (2019). Sex-specific associations between prenatal negative life events and birth outcomes. Stress, 22(6), 647-653.
56. Ryu, H. (2019). Maternal prenatal stress and birth weight (Doctoral dissertation, KDI School).
57. Steyn, K., De Wet, T., Saloojee, Y., Nel, H., & Yach, D. (2006). The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: the Birth To Ten Study. Paediatric and perinatal epidemiology, 20(2), 90-99.
58. Stone, W. L., Bailey, B., & Khraisha, N. (2014). The pathophysiology of smoking during pregnancy: a systems biology approach. Front Biosci (Elite Ed), 6(2), 318-328.
59. Thayer, Z. M., Feranil, A. B., & Kuzawa, C. W. (2012). Maternal cortisol disproportionately impacts fetal growth in male offspring: evidence from the Philippines. American Journal of Human Biology, 24(1), 1-4.
60. Therrien, A.S., Buffa, G., Roome, A., Standard, E., Taleo, G., Tarivonda, L., Olszowy, K.M. and Dancause, K.N. (2020, April). Prenatal stress predicts birthweight independent of maternal dietary patterns: results of a prospective longitudinal study in Vanuatu. In AMERICAN JOURNAL OF HUMAN BIOLOGY (Vol. 32). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.
61. Vrijkotte, T. G., Van Der Wal, M. F., Van Eijsden, M., & Bonsel, G. J. (2009). First-trimester working conditions and birthweight: a prospective cohort study. American journal of public health, 99(8), 1409-1416.
62. 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), 351-384.2
63. Whincup, P.H., Kaye, S.J., Owen, C.G., Huxley, R., Cook, D.G., Anazawa, S., Barrett-Connor, E., Bhargava, S.K., Birgisdottir, B.E., Carlsson, S., & De Rooij, S.R (2008). Birthweight and risk of type 2 diabetes: a systematic review. JAMA, 300(24), 2886-2897.

64. World Health Organization. (2019). UNICEF-WHO low birthweight estimates: levels and trends 2000-2015 (No. WHO/NMH/NHD/19.21). United Nations Children's Fund (UNICEF).
65. Zhu, P., Tao, F., Hao, J., Sun, Y., & Jiang, X. (2010). Prenatal life events stress: implications for preterm birth and infant birthweight. American journal of obstetrics and gynecology, 203(1), 34-e1.

Bibliography: Chapter 5 (BT20)

1. Abbott, P. W., Gumusoglu, S. B., Bittle, J., Beversdorf, D. Q., & Stevens, H. E. (2018). Prenatal stress and genetic risk: How prenatal stress interacts with genetics to alter risk for psychiatric illness. Psychoneuroendocrinology, 90, 9-21.
2. Abel, K. M., Wicks, S., Susser, E. S., Dalman, C., Pedersen, M. G., Mortensen, P. B., & Webb, R. T. (2010). Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies?. Archives of general psychiatry, 67(9), 923-930.
3. Adjaye-Gbewonyo, K., Avendano, M., Subramanian, S. V., & Kawachi, I. (2016). Income inequality and depressive symptoms in South Africa: a longitudinal analysis of the National Income Dynamics Study. Health & place, 42, 37-46.
4. Adonis, C. K. (2016). Exploring the salience of intergenerational trauma among children and grandchildren of victims of apartheid-era gross human rights violations. Indo-Pacific Journal of Phenomenology, 16(1-2).
5. Alexander, N., Rosenlöcher, F., Stalder, T., Linke, J., Distler, W., Morgner, J., & Kirschbaum, C. (2012). Impact of antenatal synthetic glucocorticoid exposure on endocrine stress reactivity in term-born children. The Journal of Clinical Endocrinology & Metabolism, 97(10), 3538-3544.
6. Allen, J., Balfour, R., Bell, R., & Marmot, M. (2014). Social determinants of mental health. International review of psychiatry, 26(4), 392-407.
7. Barbarin, O. A., & Richter, L. M. (2013). Mandela's children: Growing up in post-apartheid South Africa. Routledge.
8. Barker, D. J. P. (2004). The developmental origins of adult disease. Journal of the American College of Nutrition, 23(sup6), 588S-595S.
9. Betts, K. S., Williams, G. M., Najman, J. M., & Alati, R. (2015). The relationship between maternal depressive, anxious, and stress symptoms during pregnancy and adult offspring behavioural and emotional problems. Depression and Anxiety, 32(2), 82-90.
10. Bluen, S. D., & Odesnik, J. (1988). Township unrest: Development of the township life events scale. South African Journal of Psychology, 18(2), 50-57.
11. Bolten, M. I., Wurmser, H., Buske-Kirschbaum, A., Papoušek, M., Pirke, K. M., & Hellhammer, D. (2011). Cortisol levels in pregnancy as a psychobiological predictor for birthweight. Archives of women's mental health, 14(1), 33-41.
12. Bosch, N. M., Riese, H., Reijneveld, S. A., Bakker, M. P., Verhulst, F. C., Ormel, J., & Oldehinkel, A. J. (2012). Timing matters: Long term effects of adversities from prenatal period up to adolescence on adolescents' cortisol stress response. The TRAILS study. Psychoneuroendocrinology, 37(9), 1439-1447.
13. Brand, S. R., Brennan, P. A., Newport, D. J., Smith, A. K., Weiss, T., & Stowe, Z. N. (2010). The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. Psychoneuroendocrinology, 35(5), 686-693.
14. Breslau, J., Gilman, S. E., Stein, B. D., Ruder, T., Gmelin, T., & Miller, E. (2017). Sex differences in recent first-onset depression in an epidemiological sample of adolescents. Translational psychiatry, 7(5), e1139-e1139.
15. Burns, J. K. (2015). Poverty, inequality and a political economy of mental health. Epidemiology and psychiatric sciences, 24(2), 107-113.

16. Cameron, N., Richter, L., McIntyre, J., Dhlamini, N., & Garstang, L. (1996). Progress report: Teenage pregnancy and birth outcome in Soweto. Unpublished report: University of the Witwatersrand.
17. Cherak, S. J., Giesbrecht, G. F., Metcalfe, A., Ronksley, P. E., & Malebranche, M. E. (2018). The effect of gestational period on the association between maternal prenatal salivary cortisol and birth weight: a systematic review and meta-analysis. Psychoneuroendocrinology, 94, 49-62.
18. Costello, E. J., Worthman, C., Erkanli, A., & Angold, A. (2007). Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. Archives of general psychiatry, 64(3), 338-344.
19. D'Anna-Hernandez, K. L., Hoffman, M. C., Zerbe, G. O., Coussons-Read, M., Ross, R. G., & Laudenslager, M. L. (2012). Acculturation, maternal cortisol and birth outcomes in women of Mexican descent. Psychosomatic Medicine, 74(3), 296.
20. Davis, E. P., Hankin, B. L., Glynn, L. M., Head, K., Kim, D. J., & Sandman, C. A. (2020). Prenatal maternal stress, child cortical thickness, and adolescent depressive symptoms. Child development, 91(2), e432-e450.
21. de Bruijn, A. T., van Bakel, H. J., Wijnen, H., Pop, V. J., & van Baar, A. L. (2009). Prenatal maternal emotional complaints are associated with cortisol responses in toddler and preschool aged girls. Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology, 51(7), 553-563.
22. De Mola, C. L., De França, G. V. A., de Avila Quevedo, L., & Horta, B. L. (2014). Low birth weight, preterm birth and small for gestational age association with adult depression: systematic review and meta-analysis. The British Journal of Psychiatry, 205(5), 340-347.
23. Di Renzo, G. C., Rosati, A., Sarti, R. D., Cruciani, L., & Cutuli, A. M. (2007). Does fetal sex affect pregnancy outcome?. Gender medicine, 4(1), 19-30.
24. Diego, M. A., Field, T., Hernandez-Reif, M., Schanberg, S., Kuhn, C., & Gonzalez-Quintero, V. H. (2009). Prenatal depression restricts fetalgrowth. Early human development, 85(1), 65-70.
25. Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M., Griffith, J. W., & Adam, E. K. (2013). Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. Development and psychopathology, 25(3), 629-642.
26. Dunkel Schetter, C. (2011). Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annual review of psychology, 62, 531-558.
27. Dunkle, K. L., Jewkes, R. K., Brown, H. C., Yoshihama, M., Gray, G. E., McIntyre, J. A., & Harlow, S. D. (2004). Prevalence and patterns of gender-based violence and revictimization among women attending antenatal clinics in Soweto, South Africa. American journal of epidemiology, 160(3), 230-239.
28. Eleftheriades, M., Creatsas, G., & Nicolaides, K. (2006). Fetalgrowth restriction and postnatal development. Annals of the New York Academy of Sciences, 1092(1), 319-330.

29. Entringer, S. Khumsta, R. Hellhammer, H. D. Wadhwa, D. P. Wust, S. (2009). Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. Hormones and Behaviour, 55(2), 292–298. https://doi.org/10.1016/j.yhbeh.2008.11.006
30. Entringer, S., Buss, C., Rasmussen, J. M., Lindsay, K., Gillen, D. L., Cooper, D. M., & Wadhwa, P. D. (2017). Maternal cortisol during pregnancy and infant adiposity: a prospective investigation. The Journal of Clinical Endocrinology & Metabolism, 102(4), 1366-1374.
31. Feldman, P. J., Dunkel-Schetter, C., Sandman, C. A., & Wadhwa, P. D. (2000). Maternal social support predicts birth weight and fetalgrowth in human pregnancy. Psychosomatic medicine, 62(5), 715-725.
32. Field, T., Diego, M., Delgado, J., & Medina, L. (2013). Yoga and social support reduce prenatal depression, anxiety and cortisol. Journal of bodywork and movement therapies, 17(4), 397-403.
33. Filmer, D., & Pritchett, L. (1999). The effect of household wealth on educational attainment: evidence from 35 countries. Population and development review, 25(1), 85-120.
34. Gibbs, A., Jewkes, R., Willan, S., & Washington, L. (2018). Associations between poverty, mental health and substance use, gender power, and intimate partner violence amongst young (18-30) women and men in urban informal settlements in South Africa: A cross-sectional study and structural equation model. PLoS one, 13(10), e0204956.
35. Global Burden of Disease Collaborative Network. (2017). Global Burden of Disease Study 2017. Institute for Health Metrics and Evaluation (IHME). Retrieved from: https://vizhub.healthdata.org/gbd-compare/.
36. Gluckman, P. D., & Hanson, M. A. (2004, October). Maternal constraint of fetal growth and its consequences. In Seminars in fetal and neonatal medicine (Vol. 9, No. 5, pp. 419-425). WB Saunders.
37. Goel, N., Workman, J. L., Lee, T. T., Innala, L., & Viau, V. (2011). Sex differences in the HPA axis. Comprehensive Physiology, 4(3), 1121-1155.
38. Goldberg, D. P., & Hillier, V. F. (1979). A scaled version of the General Health Questionnaire. Psychological medicine, 9(1), 139-145.
39. Hammen, C., Henry, R., & Daley, S. E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. Journal of consulting and clinical psychology, 68(5), 782.
40. Hankin, B. L. (2009). Development of sex differences in depressive and co-occurring anxious symptoms during adolescence: Descriptive trajectories and potential explanations in a multiwave prospective study. Journal of Clinical Child & Adolescent Psychology, 38(4), 460-472.
41. Heim, C. M., Entringer, S., & Buss, C. (2019). Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology, 105, 123-137.
42. Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology, 33(6), 693-710.

43. Jarcho, M. R., Slavich, G. M., Tylova-Stein, H., Wolkowitz, O. M., & Burke, H. M. (2013). Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. Biological psychology, 93(1), 150-158.
44. Karlén, J., Frostell, A., Theodorsson, E., Faresjö, T., & Ludvigsson, J. (2013). Maternal influence on child HPA axis: a prospective study of cortisol levels in hair. Pediatrics, 132(5), e1333-e1340.
45. Katzow, M., Messito, M. J., Mendelsohn, A. L., Scott, M. A., & Gross, R. S. (2019). The Protective Effect of Prenatal Social Support on Infant Adiposity in the First 18 Months of Life. The Journal of pediatrics, 209, 77-84.
46. 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.
47. Kim, A. W. How should we study intergenerational trauma? Reflections on a 30-year birth cohort study in Soweto, South Africa. Somatosphere.
48. Kim, A.W., Mohamed, R.S., Kuzawa, C.K., Norris, S.A. (2020). Maternal prenatal stress during the first trimester and infant birthweight in Soweto, South Africa. In review.
49. Krontira, A. C., Cruceanu, C., & Binder, E. B. (2020). Glucocorticoids as Mediators of Adverse Outcomes of Prenatal Stress. Trends in Neurosciences.
50. Kudielka, B. M., & Kirschbaum, C. (2005). Sex differences in HPA axis responses to stress: a review. Biological psychology, 69(1), 113-132.
51. Kuzawa, C. W. (2008). The developmental origins of adult health: intergenerational inertia in adaptation and disease. In Evolution and health (pp. 325-349). Oxford University Press.
52. Ladwig, K. H., Marten-Mittag, B., Erazo, N., & Gündel, H. (2001). Identifying somatization disorder in a population-based health examination survey: psychosocial burden and gender differences. Psychosomatics, 42(6), 511-518.
53. Lærum, A. M., Reitan, S. K., Evensen, K. A. I., Lydersen, S., Brubakk, A. M., Skranes, J., & Indredavik, M. S. (2019). Psychiatric symptoms and risk factors in adults born preterm with very low birthweight or born small for gestational age at term. BMC psychiatry, 19(1), 223.
54. Lipner, E., Murphy, S. K., & Ellman, L. M. (2019). Prenatal maternal stress and the cascade of risk to schizophrenia spectrum disorders in offspring. Current psychiatry reports, 21(10), 99.
55. 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.
56. MacKinnon, N., Kingsbury, M., Mahedy, L., Evans, J., & Colman, I. (2018). The association between prenatal stress and externalizing symptoms in childhood: Evidence from the Avon Longitudinal Study of Parents and Children. Biological psychiatry, 83(2), 100-108.
57. Macleod, C. (1999). Teenage pregnancy and its 'negative'consequences: Review of South African research—Part 1. South African journal of psychology, 29(1), 1-7.
58. Maiello, S. (2001). On the transgenerational transmission of trauma and violence. Psycho-analytic Psychotherapy in South Africa, 9(2), 13-31.

59. Makola, M. P. (2011). Teenage pregnancy: views of parents/caregivers, teenagers and teachers at two high schools in Soweto, Gauteng (Doctoral dissertation).
60. Martel, M. M. (2013). Sexual selection and sex differences in the prevalence of childhood externalizing and adolescent internalizing disorders. Psychological bulletin, 139(6), 1221.
61. Maxwell, S. D., Fineberg, A. M., Drabick, D. A., Murphy, S. K., & Ellman, L. M. (2018). Maternal prenatal stress and other developmental risk factors for adolescent depression: Spotlight on sex differences. Journal of abnormal child psychology, 46(2), 381-397.
62. McQuaid, G. A., Darcey, V. L., Avalos, M. F., Fishbein, D. H., & VanMeter, J. W. (2019). Altered cortical structure and psychiatric symptom risk in adolescents exposed to maternal stress in utero: A retrospective investigation. Behavioural brain research, 375, 112145.
63. Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological psychiatry, 65(9), 732-741.
64. Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioural and biological mechanisms. Psychological bulletin, 137(6), 959.
65. Moomal, H., Jackson, P. B., Stein, D. J., Herman, A., Myer, L., Seedat, S., & Madela-Mntla, E. (2009). Perceived discrimination and mental health disorders: the South African Stress and Health study. South African Medical Journal, 99(5).
66. Myer, L., Smit, J., Roux, L. L., Parker, S., Stein, D. J., & Seedat, S. (2008). Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales. AIDS patient care and STDs, 22(2), 147-158.
67. Naninck, E. F. G., Lucassen, P. J., & Bakker, J. (2011). Sex differences in adolescent depression: do sex hormones determine vulnerability?. Journal of neuroendocrinology, 23(5), 383-392.
68. Nolen-Hoeksema, S., & Girgus, J. S. (1994). The emergence of gender differences in depression during adolescence. Psychological bulletin, 115(3), 424.
69. Norris, S. A., Richter, L. M., & Fleetwood, S. A. (2007). Panel studies in developing countries: Case analysis of sample attrition over the past 16 years within the Birth to Twenty cohort in Johannesburg, South Africa. Journal of International Development, 19, 1-8.
70. O'Donnell, K. J., Glover, V., Holbrook, J. D., & O'Connor, T. G. (2014). Maternal prenatal anxiety and child brain-derived neurotrophic factor (BDNF) genotype: effects on internalizing symptoms from 4 to 15 years of age. Development and psychopathology, 26(4pt2), 1255-1266.
71. O'Donnell, K. J., Glover, V., Jenkins, J., Browne, D., Ben-Shlomo, Y., Golding, J., & O'Connor, T. G. (2013). Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. Psychoneuroendocrinology, 38(9), 1630-1638.
72. O'Donnell, K., O'Connor, T. G., & Glover, V. (2009). Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Developmental neuroscience, 31(4), 285-292.

73. Orr, S. T. (2004). Social support and pregnancy outcome: a review of the literature. Clinical obstetrics and gynecology, 47(4), 842-855.
74. Orri, M., Gunnell, D., Richard-Devantoy, S., Bolanis, D., Boruff, J., Turecki, G., & Geoffroy, M. C. (2019). In-utero and perinatal influences on suicide risk: a systematic review and meta-analysis. The Lancet Psychiatry, 6(6), 477-492.
75. Ostlund, B. D., Conradt, E., Crowell, S. E., Tyrka, A. R., Marsit, C. J., & Lester, B. M. (2016). Prenatal stress, fearfulness, and the epigenome: exploratory analysis of sex differences in DNA methylation of the glucocorticoid receptor gene. Frontiers in behavioural neuroscience, 10, 147.
76. Panday, S., Makiwane, M., Ranchod, C., & Letsoalo, T. (2009). Teenage pregnancy in South Africa - with a specific focus on school-going learners. Child, Youth, Family and Social Development, Human Sciences Research Council. Pretoria: Department of Basic Education
77. Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. Trends in neurosciences, 31(9), 464-468.
78. Patel, V., Flisher, A. J., Hetrick, S., & McGorry, P. (2007). Mental health of young people: a global public-health challenge. The Lancet, 369(9569), 1302-1313.
79. Peltzer, K., & Pengpid, S. (2008). Sexual abuse, violence and HIV risk among adolescents in South Africa. Gender and Behaviour, 6(1), 1462-1478.
80. Perrin, M. A., Chen, H., Sandberg, D. E., Malaspina, D., & Brown, A. S. (2007). Growth trajectory during early life and risk of adult schizophrenia. The British Journal of Psychiatry, 191(6), 512-520.
81. Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Archives of general psychiatry, 55(1), 56-64.
82. Ping, E. Y., Laplante, D. P., Elgbeili, G., Hillerer, K. M., Brunet, A., O'Hara, M. W., & King, S. (2015). Prenatal maternal stress predicts stress reactivity at 2½ years of age: The Iowa Flood Study. Psychoneuroendocrinology, 56, 62-78.
83. Ping, E. Y., Laplante, D. P., Elgbeili, G., Jones, S. L., Brunet, A., & King, S. (2020). Disaster-related prenatal maternal stress predicts HPA reactivity and psychopathology in adolescent offspring: Project Ice Storm. Psychoneuroendocrinology, 104697.
84. Plant, D. T., Pawlby, S., Sharp, D., Zunszain, P. A., & Pariante, C. M. (2016). Prenatal maternal depression is associated with offspring inflammation at 25 years: a prospective longitudinal cohort study. Translational psychiatry, 6(11), e936-e936.
85. Quesada, A. A., Tristao, R. M., Pratesi, R., & Wolf, O. T. (2014). Hyper-responsiveness to acute stress, emotional problems and poorer memory in former preterm children. Stress, 17(5), 389-399.
86. Rice, F., Harold, G. T., Boivin, J., Van den Bree, M., Hay, D. F., & Thapar, A. (2010). The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. Psychological Medicine, 40(2), 335-345.
87. Richter, L. M., Norris, S. A., & Ginsburg, C. (2006). The silent truth of teenage pregnancies–Birth to Twenty cohort's next generation. South African Medical Journal, 96(2), 122.

88. Riis, J. L., Granger, D. A., Woo, H., Voegtline, K., DiPietro, J. A., & Johnson, S. B. (2019). Long-term associations between prenatal maternal cortisol and child neuroendocrine-immune regulation. International Journal of Behavioral Medicine, 1-15.
89. Rosa, M. J., Nentin, F., Bosquet Enlow, M., Hacker, M. R., Pollas, N., Coull, B., & Wright, R. J. (2019). Sex-specific associations between prenatal negative life events and birth outcomes. Stress, 22(6), 647-653.
90. Rothberg, A. D., Shuenyane, E., Lits, B., & Strebel, P. M. (1991). Effect of stress on birth weight in two Johannesburg populations. South African Medical Journal, 79(1), 35-38.
91. Ryu, H. (2019). Maternal prenatal stress and birth weight (Doctoral dissertation, KDI School).
92. Sawyer, S. M., Afifi, R. A., Bearinger, L. H., Blakemore, S. J., Dick, B., Ezeh, A. C., & Patton, G. C. (2012). Adolescence: a foundation for future health. The Lancet, 379(9826), 1630-1640.
93. Sharp, H., Hill, J., Hellier, J., & Pickles, A. (2015). Maternal antenatal anxiety, postnatal stroking and emotional problems in children: outcomes predicted from pre-and postnatal programming hypotheses. Psychological medicine, 45(2), 269-283.
94. Spann, M. N., Bansal, R., Hao, X., Rosen, T. S., & Peterson, B. S. (2020). Prenatal socioeconomic status and social support are associated with neonatal brain morphology, toddler language and psychiatric symptoms. Child Neuropsychology, 26(2), 170-188.
95. Stout SA , Espel EV , Sandman CA , Glynn LM , Davis EP . Fetalprogramming of children's obesity risk. Psychoneuroendocrinology. 2015;53:29–39.
96. Taylor, S. E. (2010). Mechanisms linking early life stress to adult health outcomes. Proceedings of the National Academy of Sciences, 107(19), 8507-8512.
97. Van den Bergh, B. R., Van Calster, B., Smits, T., Van Huffel, S., & Lagae, L. (2008). Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetalorigins of depressed mood. Neuropsychopharmacology, 33(3), 536-545.
98. Van den Bergh, B. R., van den Heuvel, M. I., Lahti, M., Braeken, M., de Rooij, S. R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S. & Schwab, M. (2017). Prenatal developmental origins of behaviour and mental health: The influence of maternal stress in pregnancy. Neuroscience & Biobehavioural Reviews.
99. Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. The Lancet Psychiatry, 3(2), 171-178.
100. Vrshek-Schallhorn, S., Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2013). The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. Psychological medicine, 43(3), 483-493.
101. Willan, S. (2013). A review of teenage pregnancy in South Africa–experiences of schooling, and knowledge and access to sexual & reproductive health services. Partners in Sexual Health, 1-63.
102. Yehuda, R., Daskalakis, N. P., Bierer, L. M., Bader, H. N., Klengel, T., Holsboer, F., & Binder, E. B. (2016). Holocaust exposure induced intergenerational effects on FKBP5 methylation. Biological psychiatry, 80(5), 372-380.
103. Zhang, B., & Wing, Y. K. (2006). Sex differences in insomnia: a meta-analysis. Sleep, 29(1), 85-93.

104. Zijlmans, M. A., Riksen-Walraven, J. M., & de Weerth, C. (2015). Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. Neuroscience & Biobehavioral Reviews, 53, 1-24.

Bibliography: Chapter 6 (CLHNS)

1. Adair, L. S., Popkin, B. M., Akin, J. S., Guilkey, D. K., Gultiano, S., Borja, J., Perez, L., Kuzawa, C. W., McDade, T., & Hindin, M. J. (2010). Cohort profile: the Cebu longitudinal health and nutrition survey. International journal of epidemiology, 40(3), 619-625.
2. Adam EK, Kumari M. 2009. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology 34:1423–1436.
3. Adam, E. K., Doane, L. D., Zinbarg, R. E., Mineka, S., Craske, M. G., & Griffith, J. W. (2010). Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. Psychoneuroendocrinology, 35(6), 921-931.
4. Angold, A., & Worthman, C. W. (1993). Puberty onset of gender differences in rates of depression: a developmental, epidemiologic and neuroendocrine perspective. Journal of Affective Disorders, 29(2), 145-158.
5. Bhagwagar, Z., Hafizi, S., Cowen, P.J., 2003. Increase in concentration of waking salivary cortisol in recovered patients with depression. American Journal Psychiatry 160, 1890–1891.
6. Breier, A. (1989). Experimental approaches to human stress research: Assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. Biological Psychiatry, 26, 438 – 462.
7. Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults.
8. Cărnuţă, M., Crişan, L. G., Vulturar, R., Opre, A., & Miu, A. C. (2015). Emotional non-acceptance links early life stress and blunted cortisol reactivity to social threat. Psychoneuroendocrinology, 51, 176-187.
9. Carpenter, L. L., Shattuck, T. T., Tyrka, A. R., Geracioti, T. D., & Price, L. H. (2011). Effect of childhood physical abuse on cortisol stress response. Psychopharmacology, 214(1), 367-375.
10. Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., Wier, L.M., Mello, A.F., Mello, M.F., Anderson, G.M., Wilkinson, C.W., Price, L.H., 2007. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. Biol. Psychiatry 62, 1080–1087.
11. Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. Journal of affective disorders, 82(2), 217-225.
12. Chida, Y., & Steptoe, A. (2009). Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. Biological psychology, 80(3), 265-278.
13. Cohen, S., Kamarck, T., & Mermelstein, R. (1994). Perceived stress scale. Measuring stress: A guide for health and social scientists.
14. Coplan, J. D. et al. Persistent elevations of cerebrospinal fluid concentrations of corticotropinreleasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc. Natl Acad. Sci. USA 93, 1619–1623 (1996).
15. Dahl, R. E., Ryan, N. D., Puig-Antich, J., Nguyen, N. A., Al-Shabbout, M., Meyer, V. A., & Perel, J. (1991). 24-hour cortisol measures in adolescents with major depression: a controlled study. Biological Psychiatry, 30(1), 25-36.

16. DeSantis, A. S., Kuzawa, C. W., & Adam, E. K. (2015). Developmental origins of flatter cortisol rhythms: socioeconomic status and adult cortisol activity. American Journal of Human Biology, 27(4), 458-467.
17. Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M., Griffith, J. W., & Adam, E. K. (2013). Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. Development and psychopathology, 25(3), 629-642.
18. Dong, M., Giles, W. H., Felitti, V. J., Dube, S. R., Williams, J. E., Chapman, D. P., & Anda, R. F. (2004). Insights into causal pathways for ischemic heart disease. Circulation, 110(13), 1761-1766.
19. Dube, S. R., Fairweather, D., Pearson, W. S., Felitti, V. J., Anda, R. F., & Croft, J. B. (2009). Cumulative childhood stress and autoimmune diseases in adults. Psychosomatic medicine, 71(2), 243.
20. Elzinga, B. M., Roelofs, K., Tollenaar, M. S., Bakvis, P., van Pelt, J., & Spinhoven, P. (2008). Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: a study among healthy young subjects. Psychoneuroendocrinology, 33(2), 227-237.
21. Fanos, J. H., & Nickerson, B. G. (1991). Long-term effects of sibling death during adolescence. Journal of Adolescent Research, 6(1), 70-82.
22. Fogelman, N., & Canli, T. (2018). Early life stress and cortisol: A meta-analysis. Hormones and behavior, 98, 63-76.
23. Gold, P.W., Goodwin, F.K. & Chrousos, G. P. (1988) Clinical and biochemical manifestations of depression. Relation to neurobiology of stress. New England Journal of Medicine, 319, 413 -420.
24. Gonzalez, A., Jenkins, J. M., Steiner, M., & Fleming, A. S. (2009). The relation between early life adversity, cortisol awakening response and diurnal salivary cortisol levels in postpartum women. Psychoneuroendocrinology, 34(1), 76-86.
25. Goodyer, I. M., Herbert, J., Altham, P.M.E., et al (1996) Adrenal secretion during major depression in 8 to 16 year-olds. I. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. Psychological Medicine, 26, 245 -256.
26. Gustafsson, P. E., Janlert, U., Theorell, T., & Hammarström, A. (2010). Life-course socioeconomic trajectories and diurnal cortisol regulation in adulthood. Psychoneuroendocrinology, 35(4), 613-623.
27. Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. Experimental neurology, 233(1), 102-111.
28. Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., Miller, A. H., & Nemeroff, C. B. (2000). Pituitary – adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. Journal of the American Medical Association, 284, 592 – 597.
29. Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology, 33(6), 693-710.
30. Hindin, M. J. (2005). Family dynamics, gender differences and educational attainment in Filipino adolescents. Journal of adolescence, 28(3), 299-316.

31. Hindin, M. J., & Gultiano, S. (2006). Associations between witnessing parental domestic violence and experiencing depressive symptoms in Filipino adolescents. American journal of public health, 96(4), 660-663.
32. Hock, R. S., Hindin, M. J., Bass, J. K., Surkan, P. J., Bradshaw, C. P., & Mendelson, T. (2016). Parenting styles and emerging adult drug use in Cebu, the Philippines. International journal of culture and mental health, 9(2), 108-119.4
33. Hostinar, C. E., Sullivan, R. M., & Gunnar, M. R. (2014). Psychobiological mechanisms underlying the social buffering of the hypothalamic–pituitary–adrenocortical axis: A review of animal models and human studies across development. Psychological bulletin, 140(1), 256.
34. Janusek, L. W., Tell, D., Gaylord-Harden, N., & Mathews, H. L. (2017). Relationship of childhood adversity and neighborhood violence to a proinflammatory phenotype in emerging adult African American men: an epigenetic link. Brain, behavior, and immunity, 60, 126-135.
35. Kendler, K. S., Heath, A. C., & Eaves, J. (1992). Psychopathology in Women. Arch Gen Psychiatry, 49, 109-116.
36. Koss, K. J., & Gunnar, M. R. (2017). Annual Research Review: Early adversity, the hypothalamic–pituitary–adrenocortical axis, and child psychopathology. Journal of Child Psychology and Psychiatry.
37. Kudielka BM, Kirschbaum C. (2003). Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology 28:35–47.
38. Lovallo, W. R., Farag, N. H., Sorocco, K. H., Cohoon, A. J., & Vincent, A. S. (2012). Lifetime adversity leads to blunted stress axis reactivity: studies from the Oklahoma Family Health Patterns Project. Biological psychiatry, 71(4), 344-349.
39. Luecken, L. J. (2000). Parental caring and loss during childhood and adult cortisol responses to stress. Psychology and Health, 15, 841 – 851.
40. Luecken, L. J., & Fabricius, B. (2003). Physical health vulnerability in adult children from divorced and intact families. Journal of Psychosomatic Research, 55, 221 – 228.
41. Luecken, L.J., Appelhans, B.M. (2006). Early parental loss and salivary cortisol in young adulthood: the moderating role of family environment. Dev. Psychopathol. 18, 295—308.
42. Luecken, L.J., Lemery, K.S. (2004). Early caregiving and physiological stress response. Clin. Psychol. Rev. 24, 171—191.
43. Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature reviews neuroscience, 10(6), 434.
44. Lyons, D. M., & Parker, K. J. (2007). Stress inoculation-induced indications of resilience in monkeys. Journal of traumatic stress, 20(4), 423-433.
45. Mastorakos G, Ilias I. 2000. Maternal hypothalamic-pituitary-adrenal axis in pregnancy and the postpartum period: postpartum-related disorders. Ann NY Acad Sci 900:95–106.
46. Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological psychiatry, 65(9), 732-741.
47. Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological bulletin, 133(1), 25.

48. Nicolson, N. A. (2004). Childhood parental loss and cortisol levels in adult men. Psychoneuroendocrinology, 29(8), 1012-1018.
49. Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. Trends in neurosciences, 31(9), 464-468.
50. Pesonen, A.K., Raikkonen, K., Feldt, K., Heinonen, K., Osmond, C., Phillips, D.I., Barker, D.J., Eriksson, J.G., Kajantie, E., 2010. Childhood separation experience predicts HPA axis hormonal responses in late adulthood: a natural experiment of World War II. Psychoneuroendocrinology 35, 758–767.
51. Plotsky, P. M., Owens, M. J., & Nemeroff, C. B. (1998). Psychoneuroendocrinology of depression: hypothalamic-pituitary-adrenal axis. Psychiatric Clinics of North America, 21(2), 293-307.
52. Pruessner, M., Hellhammer, D. H., Pruessner, J. C., & Lupien, S. J. (2003). Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. Psychosomatic medicine, 65(1), 92-99.
53. Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. Applied psychological measurement, 1(3), 385-401.
54. Sanchez, M. M. et al. Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. Biol. Psychiatry 57, 373–381 (2005).
55. Schalinski, I., Elbert, T., Steudte-Schmiedgen, S., & Kirschbaum, C. (2015). The cortisol paradox of trauma-related disorders: lower phasic responses but higher tonic levels of cortisol are associated with sexual abuse in childhood. PloS one, 10(8), e0136921.
56. Shea, A., Walsh, C., MacMillan, H., & Steiner, M. (2005). Child maltreatment and HPA axis dysregulation: relationship to major depressive disorder and post traumatic stress disorder in females. Psychoneuroendocrinology, 30(2), 162-178.
57. Tarullo, A. R., & Gunnar, M. R. (2006). Child maltreatment and the developing HPA axis. Hormones and behavior, 50(4), 632-639.
58. Taylor, S. E., Way, B. M., & Seeman, T. E. (2011). Early adversity and adult health outcomes. Development and psychopathology, 23(3), 939-954.
59. Trickett PK, Noll JG, Susman EJ, Shenk CE, Putnam FW. (2010). Attenuation of cortisol across development for victims of sexual abuse. Dev Psychopathol 22:165–75.
60. Tyrka, A. R., Wier, L., Price, L. H., Ross, N. S., & Carpenter, L. L. (2008). Childhood parental loss and adult psychopathology: effects of loss characteristics and contextual factors. The International Journal of Psychiatry in Medicine, 38(3), 329-344.
61. Tyrka, A. R., Wier, L., Price, L. H., Ross, N., Anderson, G. M., Wilkinson, C. W., & Carpenter, L. L. (2008). Childhood parental loss and adult hypothalamic-pituitary-adrenal function. Biological psychiatry, 63(12), 1147-1154.
62. Vaccarino, O., Levitan, R., Ravindran, A., 2015. The cortisol response to social stress in social anxiety disorder. Asian J. Psychiatr. 14, 57–60.
63. van der Vegt, E. J., Van Der Ende, J., Kirschbaum, C., Verhulst, F. C., & Tiemeier, H. (2009). Early neglect and abuse predict diurnal cortisol patterns in adults: A study of international adoptees. Psychoneuroendocrinology, 34(5), 660-669.
64. Young, E. A., Haskett, R. F., Grunhaus, L., Pande, A., Weinberg, V. M., Watson, S. J., & Akil, H. (1994). Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. Archives of General Psychiatry, 51(9), 7.

Bibliography: Chapter 7 (Discussion)

1. Abel, K. M., Wicks, S., Susser, E. S., Dalman, C., Pedersen, M. G., Mortensen, P. B., & Webb, R. T. (2010). Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies?. Archives of general psychiatry, 67(9), 923-930.
2. Antonelli, M. C., Pallarés, M. E., Ceccatelli, S., & Spulber, S. (2017). Long-term consequences of prenatal stress and neurotoxicants exposure on neurodevelopment. Progress in neurobiology, 155, 21-35.
3. Atmore, E. (2013). Early childhood development in South Africa–progress since the end of apartheid. International Journal of Early Years Education, 21(2-3), 152-162.
4. Bandoli, G., Jelliffe-Pawlowski, L. L., Feuer, S. K., Liang, L., Oltman, S. P., Paynter, R., ... & Chambers, C. D. (2018). Second trimester serum cortisol and preterm birth: an analysis by timing and subtype. Journal of Perinatology, 38(8), 973-981.
5. Barker, E. D., Walton, E., & Cecil, C. A. (2018). Annual Research Review: DNA methylation as a mediator in the association between risk exposure and child and adolescent psychopathology. Journal of Child Psychology and Psychiatry, 59(4), 303-322.
6. Berghänel, A., Heistermann, M., Schülke, O., & Ostner, J. (2017). Prenatal stress accelerates offspring growth to compensate for reduced maternal investment across mammals. Proceedings of the National Academy of Sciences, 114(50), E10658-E10666.
7. Bilbo, S. D., & Schwarz, J. M. (2009). Early-life programming of later-life brain and behavior: a critical role for the immune system. Frontiers in behavioral neuroscience, 3, 14.
8. Bhuiyan, A. R., Srinivasan, S. R., Chen, W., Azevedo, M. J., & Berenson, G. S. (2011). Influence of low birth weight on C-reactive protein in asymptomatic younger adults: the bogalusa heart study. BMC research notes, 4(1), 1-5.
9. Bjuland, K. J., Rimol, L. M., Løhaugen, G. C., & Skranes, J. (2014). Brain volumes and cognitive function in very-low-birth-weight (VLBW) young adults. European Journal of Paediatric Neurology, 18(5), 578-590.
10. Braithwaite, E. C., Kundakovic, M., Ramchandani, P. G., Murphy, S. E., & Champagne, F. A. (2015). Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. Epigenetics, 10(5), 408-417.
11. Buss, C., Lord, C., Wadiwalla, M., Hellhammer, D. H., Lupien, S. J., Meaney, M. J., & Pruessner, J. C. (2007). Maternal care modulates the relationship between prenatal risk and hippocampal volume in women but not in men. Journal of Neuroscience, 27(10), 2592-2595.
12. Cohen, S., Janicki-Deverts, D., Doyle, W. J., Miller, G. E., Frank, E., Rabin, B. S., & Turner, R. B. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proceedings of the National Academy of Sciences, 109(16), 5995-5999.
13. Conradt, E., Hawes, K., Guerin, D., Armstrong, D. A., Marsit, C. J., Tronick, E., & Lester, B. M. (2016). The contributions of maternal sensitivity and maternal depressive symptoms to epigenetic processes and neuroendocrine functioning. Child Development, 87, 73–85

14. Damian, D. J., Njau, B., Lisasi, E., Msuya, S. E., & Boulle, A. (2019). Trends in maternal and neonatal mortality in South Africa: a systematic review. Systematic reviews, 8(1), 76.
15. Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., … Lindner, C. (2012). Limbic scars: Long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biological Psychiatry, 71(4), 286–293.
16. Devlin, A. M., Brain, U., Austin, J., & Oberlander, T. F. (2010). Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. PLoS ONE, 5, 2–9.
17. Dunkel Schetter, C. (2011). Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annual review of psychology, 62, 531-558.
18. Ellman, L. M., Murphy, S. K., Maxwell, S. D., Calvo, E. M., Cooper, T., Schaefer, C. A., ... & Brown, A. S. (2019). Maternal cortisol during pregnancy and offspring schizophrenia: Influence of fetal sex and timing of exposure. Schizophrenia research, 213, 15-22.
19. Entringer, S., Kumsta, R., Nelson, E. L., Hellhammer, D. H., Wadhwa, P. D., & Wüst, S. (2008). Influence of prenatal psychosocial stress on cytokine production in adult women. Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology, 50(6), 579-587.
20. Ernst, M., Reiner, I., Fieß, A., Tibubos, A. N., Schulz, A., Burghardt, J., ... & König, J. (2020). Sex-dependent associations of low birth weight and suicidal ideation in adulthood: a community-based cohort study. Scientific Reports, 10(1), 1-11.
21. Evans, G. W., & Kim, P. (2013). Childhood poverty, chronic stress, self-regulation, and coping. Child development perspectives, 7(1), 43-48.
22. Farajdokht, F., Sadigh-Eteghad, S., Dehghani, R., Mohaddes, G., Abedi, L., Bughchechi, R., ... & Mahmoudi, J. (2017). Very low birth weight is associated with brain structure abnormalities and cognitive function impairments: A systematic review. Brain and cognition, 118, 80-89.
23. Flouri, E., Francesconi, M., Midouhas, E., & Lewis, G. (2020). Prenatal and childhood adverse life events, inflammation and depressive symptoms across adolescence. Journal of Affective Disorders, 260, 577-582.
24. Fogelman, N., & Canli, T. (2018). Early life stress and cortisol: a meta-analysis. Hormones and behavior, 98, 63-76.
25. Folkman, S., & Lazarus, R. S. (1986). Stress processes and depressive symptomatology. Journal of abnormal psychology, 95(2), 107. doi: 10.1037/0021-843X.95.2.107.
26. Frisancho, A. R. (2009). Developmental adaptation: where we go from here. American Journal of Human Biology: The Official Journal of the Human Biology Association, 21(5), 694-703.

27. Glover, V., & Hill, J. (2012). Sex differences in the programming effects of prenatal stress on psychopathology and stress responses: an evolutionary perspective. Physiology & Behavior, 106(5), 736-740.
28. Glover, V., O'Donnell, K. J., O'Connor, T. G., & Fisher, J. (2018). Prenatal maternal stress, fetal programming, and mechanisms underlying later psychopathology—a global perspective. Development and Psychopathology, 30(3), 843-854.
29. Gluckman, P. D., Hanson, M. A., & Beedle, A. S. (2007). Early life events and their consequences for later disease: a life history and evolutionary perspective. American Journal of Human Biology, 19(1), 1-19.
30. Goldstein, J. M., Hale, T., Foster, S. L., Tobet, S. A., & Handa, R. J. (2019). Sex differences in major depression and comorbidity of cardiometabolic disorders: impact of prenatal stress and immune exposures. Neuropsychopharmacology, 44(1), 59-70.
31. Gouin, J. P., Hantsoo, L., & Kiecolt-Glaser, J. K. (2008). Immune dysregulation and chronic stress among older adults: a review. Neuroimmunomodulation, 15(4-6), 251-259.
32. Hantsoo, L., Kornfield, S., Anguera, M. C., & Epperson, C. N. (2019). Inflammation: a proposed intermediary between maternal stress and offspring neuropsychiatric risk. Biological psychiatry, 85(2), 97-106.
33. Henrichs, J., Schenk, J., Roza, S., Lambregtse-van den Berg, M., Schmidt, H., Steegers, E., ... & Tiemeier, H. (2010). Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychological medicine, 40(4), 633-643.
34. Hill, Austin Bradford (1965). "The Environment and Disease: Association or Causation?". Proceedings of the Royal Society of Medicine. 58 (5): 295–300.
35. Ilg, L., Kirschbaum, C., Li, S. C., Rosenlöcher, F., Miller, R., & Alexander, N. (2019). Persistent effects of antenatal synthetic glucocorticoids on endocrine stress reactivity from childhood to adolescence. The Journal of Clinical Endocrinology & Metabolism, 104(3), 827-834.
36. Jacobsen, G., Schei, B., & Hoffman, H. J. (1997). Psychosocial factors and small-for-gestational-age infants among parous Scandinavian women. Acta obstetricia et gynecologica Scandinavica. Supplement, 165, 14-18.
37. Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. Neuroscience & Biobehavioral Reviews, 35(1), 2-16.
38. Kendler, K. S., Kuhn, J. W., & Prescott, C. A. (2004). Childhood sexual abuse, stressful life events and risk for major depression in women. Psychological Medicine, 34(8), 1475–1482.
39. Kendler, K. S., Kuhn, J. W., & Prescott, C. A. (2004). Childhood sexual abuse, stressful life events and risk for major depression in women. Psychological Medicine, 34(8), 1475–1482.
40. Kertes, D. A., Bhatt, S. S., Kamin, H. S., Hughes, D. A., Rodney, N. C., & Mulligan, C. J. (2017). BNDF methylation in mothers and newborns is associated with maternal exposure to war trauma. Clinical epigenetics, 9(1), 68.

41. Kim, A. W. (2020a). Promoting mental health in community and research settings during COVID-19: Perspectives and experiences from Soweto, South Africa. American Journal of Human Biology, 32(5), e23509.
42. Kim, A. W. (2020b). How should we study intergenerational trauma? Reflections on a 30-year birth cohort study in Soweto, South Africa.
43. Kim, A. W., Kaiser, B., Bosire, E., Shahbazian, K., & Mendenhall, E. (2019). Idioms of resilience among cancer patients in urban South Africa: An anthropological heuristic for the study of culture and resilience. Transcultural psychiatry, 56(4), 720-747.
44. Kim, A. W., Nyengerai, T., & Mendenhall, E. (2020). Evaluating the mental health impacts of the COVID-19 pandemic: perceived risk of COVID-19 infection and childhood trauma predict adult depressive symptoms in urban South Africa. Psychological Medicine, 1-24.
45. Kratimenos, P., & Penn, A. A. (2019). Placental programming of neuropsychiatric disease. Pediatric research, 86(2), 157-164.
46. Kuzawa, C. W. (2020). Pregnancy as an intergenerational conduit of adversity: How nutritional and psychosocial stressors reflect different historical timescales of maternal experience. Current Opinion in Behavioral Sciences, 36, 42-47.
47. Lærum, A. M., Reitan, S. K., Evensen, K. A. I., Lydersen, S., Brubakk, A. M., Skranes, J., & Indredavik, M. S. (2017). Psychiatric disorders and general functioning in low birth weight adults: a longitudinal study. Pediatrics, 139(2).
48. Lindsay, K. L., Buss, C., Wadhwa, P. D., & Entringer, S. (2019). The interplay between nutrition and stress in pregnancy: implications for fetal programming of brain development. Biological psychiatry, 85(2), 135-149.
49. Mandelli, L., Petrelli, C., & Serretti, A. (2015). The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. European Psychiatry, 30(6), 665–680.
50. Mathewson, K. J., Chow, C. H., Dobson, K. G., Pope, E. I., Schmidt, L. A., & Van Lieshout, R. J. (2017). Mental health of extremely low birth weight survivors: a systematic review and meta-analysis. Psychological bulletin, 143(4), 347.
51. Medrano, M. A., & Hatch, J. P. (2005). Childhood trauma, sexually transmitted diseases and the perceived risk of contracting HIV in a drug using population. The American Journal of Drug and Alcohol Abuse, 31(3), 403–416.
52. Meloni, M. (2016). Political biology: Science and social values in human heredity from eugenics to epigenetics. Springer.
53. Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological bulletin, 133(1), 25.
54. Monk, C., Feng, T., Lee, S., Krupska, I., Champagne, F. A., & Tycko, B. (2016). Distress during pregnancy: Epigenetic regulation of placenta glucocorticoid-related genes and fetal neurobehavior. The American Journal of Psychiatry, 7, 705–713.

55. Morsing, E., Åsard, M., Ley, D., Stjernqvist, K., & Maršál, K. (2011). Cognitive function after intrauterine growth restriction and very preterm birth. Pediatrics, 127(4), e874-e882.
56. Moshabela, M., Bukenya, D., Darong, G., Wamoyi, J., McLean, E., Skovdal, M., ... & Hosegood, V. (2017). Traditional healers, faith healers and medical practitioners: the contribution of medical pluralism to bottlenecks along the cascade of care for HIV/AIDS in Eastern and Southern Africa. Sexually Transmitted Infections, 93(Suppl 3).
57. Müller, N., Krause, D., Barth, R., Myint, A. M., Weidinger, E., Stettinger, W., … Schwarz, M. J. (2019). Childhood adversity and current stress are related to pro-and anti-inflammatory cytokines in major depression. Journal of Affective Disorders, 253, 270–276.
58. Mulligan, C. J. (2016). Early environments, stress, and the epigenetics of human health. Annual Review of Anthropology, 45, 233-249.
59. 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.
60. Nast, I., Bolten, M., Meinlschmidt, G., & Hellhammer, D. H. (2013). How to measure prenatal stress? A systematic review of psychometric instruments to assess psychosocial stress during pregnancy. Paediatric and perinatal epidemiology, 27(4), 313-322.
61. Navigating Transitions in Hypothalamic–Pituitary–Adrenal Function from Pregnancy Through Lactation: Implications for Maternal Health and Infant Brain Development
62. O'Donnell, K. J., & Meaney, M. J. (2017). Fetal origins of mental health: the developmental origins of health and disease hypothesis. American Journal of Psychiatry, 174(4), 319-328.
63. O'Donnell, K., O'connor, T. G., & Glover, V. (2009). Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Developmental neuroscience, 31(4), 285-292.
64. Opel, N., Redlich, R., Zwanzger, P., Grotegerd, D., Arolt, V., Heindel, W., … Dannlowski, U. (2014). Hippocampal atrophy in major depression: A function of childhood maltreatment rather than diagnosis? Neuropsychopharmacology, 39(12), 2723–2731.
65. 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), 531-535.2
66. Peacock, N. (1991). An evolutionary perspective on the patterning of maternal investment in pregnancy. Human Nature, 2(4), 351-385.
67. Peterson, C., & Seligman, M. E. (1983). Learned helplessness and victimization. Journal of Social Issues, 39(2), 103–116.
68. Phillips, D. I., Walker, B. R., Reynolds, R. M., Flanagan, D. E., Wood, P. J., Osmond, C., ... & Whorwood, C. B. (2000). Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. Hypertension, 35(6), 1301-1306.
69. Ping, E. Y., Laplante, D. P., Elgbeili, G., Jones, S. L., Brunet, A., & King, S. (2020). Disaster-related prenatal maternal stress predicts HPA reactivity and psychopathology in adolescent offspring: Project Ice Storm. Psychoneuroendocrinology, 104697.

70. Plant, D. T., Pawlby, S., Sharp, D., Zunszain, P. A., & Pariante, C. M. (2016). Prenatal maternal depression is associated with offspring inflammation at 25 years: a prospective longitudinal cohort study. Translational psychiatry, 6(11), e936-e936.
71. Provenzi, L., Brambilla, M., Scotto di Minico, G., Montirosso, R., & Borgatti, R. (2020). Maternal caregiving and DNA methylation in human infants and children: Systematic review. Genes, Brain and Behavior, 19(3), e12616.
72. Räikkönen, K., Pesonen, A. K., Roseboom, T. J., & Eriksson, J. G. (2012). Early determinants of mental health. Best Practice & Research Clinical Endocrinology & Metabolism, 26(5), 599-611.
73. Raznahan, A., Greenstein, D., Lee, N. R., Clasen, L. S., & Giedd, J. N. (2012). Prenatal growth in humans and postnatal brain maturation into late adolescence. Proceedings of the National Academy of Sciences, 109(28), 11366-11371.
74. Rich, E. L., & Romero, L. M. (2005). Exposure to chronic stress downregulates corticosterone responses to acute stressors. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 288(6), R1628-R1636.
75. Richter, L. M., Mathews, S., Kagura, J., & Nonterah, E. (2018). A longitudinal perspective on violence in the lives of South African children from the Birth to Twenty Plus cohort study in Johannesburg-Soweto. South African Medical Journal, 108(3), 181-186.
76. Richter, L., Norris, S., Pettifor, J., Yach, D., & Cameron, N. (2007). Cohort profile: Mandela's children: the 1990 Birth to Twenty study in South Africa. International journal of epidemiology, 36(3), 504-511.
77. Robertson, L. J., Janse van Rensburg, B., Talatala, M., Chambers, C., Sunkel, C., Patel, B., & Stevenson, S. (2018). Unpacking Recommendation 16 of the Health Ombud's report on the Life Esidimeni tragedy. SAMJ: South African Medical Journal, 108(5), 362-363.
78. Rohleder, N. (2019). Stress and inflammation–The need to address the gap in the transition between acute and chronic stress effects. Psychoneuroendocrinology, 105, 164-171.
79. Rosa, M. J., Nentin, F., Bosquet Enlow, M., Hacker, M. R., Pollas, N., Coull, B., & Wright, R. J. (2019). Sex-specific associations between prenatal negative life events and birth outcomes. Stress, 22(6), 647-653.
80. Ryu, H. (2019). Maternal prenatal stress and birth weight (Doctoral dissertation, KDI School).
81. Sandman, C. A. (2018). Prenatal CRH: an integrating signal of fetal distress. Development and psychopathology, 30(3), 941-952.
82. Schlotz, W., & Phillips, D. I. (2009). Fetal origins of mental health: evidence and mechanisms. Brain, behavior, and immunity, 23(7), 905-916.
83. Sheehan, T. J. (1998). Stress and low birth weight: a structural modeling approach using real life stressors. Social science & medicine, 47(10), 1503-1512.
84. Singh, G. K., Kenney, M. K., Ghandour, R. M., Kogan, M. D., & Lu, M. C. (2013). Mental health outcomes in US children and adolescents born prematurely or with low birthweight. Depression research and treatment, 2013.

85. Slopen, N., Loucks, E. B., Appleton, A. A., Kawachi, I., Kubzansky, L. D., Non, A. L., ... & Gilman, S. E. (2015). Early origins of inflammation: An examination of prenatal and childhood social adversity in a prospective cohort study. Psychoneuroendocrinology, 51, 403-413.
86. Sorsdahl, K., Stein, D. J., & Flisher, A. J. (2010). Traditional healer attitudes and beliefs regarding referral of the mentally ill to Western doctors in South Africa. Transcultural Psychiatry, 47(4), 591-609.
87. Sosnowski, D. W., Booth, C., York, T. P., Amstadter, A. B., & Kliewer, W. (2018). Maternal prenatal stress and infant DNA methylation: a systematic review. Developmental psychobiology, 60(2), 127-139.
88. South Africa Department of Health. (2015). Guidelines for maternity care in South Africa: a manual for clinics, community health centres and district hospitals. Department of Health.
89. Stroud, C. B., Davila, J., Hammen, C., & Vrshek-Schallhorn, S. (2011). Severe and nonsevere events in first onsets versus recurrences of depression: Evidence for stress sensitization. Journal of Abnormal Psychology, 120(1), 142.
90. Sutherland, S., & Brunwasser, S. M. (2018). Sex differences in vulnerability to prenatal stress: a review of the recent literature. Current psychiatry reports, 20(11), 102.
91. Taylor, H. G., Filipek, P. A., Juranek, J., Bangert, B., Minich, N., & Hack, M. (2011). Brain volumes in adolescents with very low birth weight: effects on brain structure and associations with neuropsychological outcomes. Developmental neuropsychology, 36(1), 96-117.
92. Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. Nature Reviews Neuroscience, 17(10), 652.
93. Thomas, K., Harrison, G., Zammit, S., Lewis, G., Horwood, J., Heron, J., ... & Gunnell, D. (2009). Association of measures of fetal and childhood growth with non-clinical psychotic symptoms in 12-year-olds: the ALSPAC cohort. The British Journal of Psychiatry, 194(6), 521-526.
94. Ting, J. Y., Kingdom, J. C., & Shah, P. S. (2018). Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age. American Journal of Obstetrics and Gynecology, 218(2), S818-S828.
95. Unternaehrer, E., Bolten, M., Nast, I., Staehli, S., Meyer, A. H., Dempster, E., ... & Meinlschmidt, G. (2016). Maternal adversities during pregnancy and cord blood oxytocin receptor (OXTR) DNA methylation. Social cognitive and affective neuroscience, 11(9), 1460-1470.
96. Van Lieshout, R. J., Boyle, M. H., Favotto, L., Krzeczkowski, J. E., Savoy, C., Saigal, S., & Schmidt, L. A. (2018). Impact of extremely low-birth-weight status on risk and resilience for depression and anxiety in adulthood. Journal of Child Psychology and Psychiatry, 59(5), 596-603.

97. Wabiri, N., Chersich, M., Shisana, O., Blaauw, D., Rees, H., & Dwane, N. (2016). Growing inequities in maternal health in South Africa: a comparison of serial national household surveys. BMC pregnancy and childbirth, 16(1), 256.
98. Wadhwa P, Buss C, Entringer S, Swanson J. (2009). Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med 27: 358–368
99. 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), 351-384.2
100. Walsh, K., McCormack, C. A., Webster, R., Pinto, A., Lee, S., Feng, T., ... & Werner, E. A. (2019). Maternal prenatal stress phenotypes associate with fetal neurodevelopment and birth outcomes. Proceedings of the National Academy of Sciences, 116(48), 23996-24005.
101. Wells, J. C. (2018). Life history trade-offs and the partitioning of maternal investment: implications for health of mothers and offspring. Evolution, medicine, and public health, 2018(1), 153-166.
102. Ye, J., Wu, C., Chu, X., Wen, Y., Li, P., Cheng, B., ... & Qi, X. (2020). Evaluating the effect of birth weight on brain volumes and depression: An observational and genetic study using UK Biobank cohort. European Psychiatry, 63(1).
103. Zijlmans, M. A., Riksen-Walraven, J. M., & de Weerth, C. (2015). Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. Neuroscience & Biobehavioral Reviews

CURRICULUM VITAE

Andrew Wooyoung Kim
Northwestern University
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Evanston, Illinois 60208 USA
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Education

2016 – 2020 Ph.D. Anthropology (Biological/Medical)
Graduate Certificate in Society, Biology, and Health
Graduate Certificate in Transdisciplinary Developmental Sciences
Northwestern University (Evanston, Illinois, USA)
Advisor: Christopher Kuzawa
Committee members: Thomas McDade, Emma Adam, Shane Norris

2011-2015B.S. Anthropology & Human Biology, minor in Global Development
Emory University (Atlanta, Georgia, USA)

Academic interests

Intergenerational mechanisms of stress transmission; biological anthropology & human biology; racial justice; global mental health; stress physiology; developmental origins of health and disease; epigenetics; critical public health; cross-cultural psychiatry; biocultural anthropology; critical medical anthropology

Appointments

12/20 (Upcoming)	Postdoctoral Research Fellow, Chester Pierce Division of Global Psychiatry at the Massachusetts General Hospital & Department of Psychiatry at Harvard Medical School, Boston, USA
12/20 (Upcoming)	Honorary Lecturer, South Africa Medical Research Council Developmental Pathways for Health Research Unit, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa
07/19 – Present	Research Fellow, The South African Depression and Anxiety Group (SADAG), Johannesburg, South Africa
07/19 – Present	National Institutes of Health Fogarty Global Health Fellow, Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, USA
03/19 – Present	Graduate Fellow, Program in Global Health Studies, Northwestern University, Evanston, USA
08/18 – 12/20	Honorary Associate Researcher, South Africa Medical Research Council Developmental Pathways for Health Research Unit, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa

External Fellowships and Awards

2016-current	Graduate Research Fellowship, National Science Foundation (NSF-GRFP) ($34,000 stipend and $12,000 cost of education allowance for three years)
2014-current	Mellon Mays Undergraduate Fellowship, Social Science Research Council, Andrew W. Mellon Foundation ($12,000)
2019	William S. Pollitzer Student Travel Award, 88th Annual Meeting for the American Association of Biological Anthropologists, Cleveland, OH ($500)
2019	Alternate, Fulbright U.S. Student Program (South Africa), Institute for International Education
2018	Oshinsky-McKern Award for Best Student Podium Presentation, 46th Annual Meeting for the Canadian Association for Physical Anthropology, London, ON ($370)
2017	Student Member Travel Award, Human Biology Association ($500)
2015-16	Emerson National Hunger Fellowship, Congressional Hunger Center
2011	1st Place and Best in Category: Behavior and Social Sciences, 2011 Intel International Science and Engineering Fair, Society for Science & the Public ($8,000)
2011	Dudley R. Herschbach Stockholm International Youth Science Seminar Award, 2011 Intel International Science and Engineering Fair, Society for Science & the Public
2011	Psi Chi: International Honor Society in Psychology Research Award, 2010 Intel International Science and Engineering Fair, Society for Science & the Public ($400)
2011	Scholar, Coca-Cola Scholars Foundation ($10,000)

Internal Fellowship and Awards

2019	Graduate Affiliate, Program in Global Health Studies, Northwestern University ($1000)
2018	Graduate Affiliate, Science and Human Culture Program
2018	Graduate Student Conference Travel Award, Buffett Institute for Global Studies ($400)
2017	Institute for Innovations in Developmental Science Cluster (DevSci) Cluster, Feinberg School of Medicine
2017	Society, Biology, Health Cluster Fellow, Cells to Society (C2S): The Center on Social Disparities and Health, Institute for Policy Research
2017	University Fellowship, The Graduate School ($30,000 for five years)
2015	Outstanding Senior Award, Department of Anthropology, Emory University ($500)
2013-15	Dean's List, Emory College of Arts and Sciences

External Grants

9/19 – current	Dissertation Fieldwork Grant, Wenner-Gren Foundation for Anthropological Research ($14,325) http://www.wennergren.org/grantees/kim-andrew-wooyoung
9/19 - current	Doctoral Dissertation Research Improvement Grant, Biological Anthropology Program, National Science Foundation ($29,434) https://www.nsf.gov/awardsearch/showAward?AWD_ID=1849265
9/19 - current	HBNU Fogarty Global Training Program Fellowship, Fogarty International Center, National Institutes of Health ($39,451) https://sites.sph.harvard.edu/global-health-research-partnership/2019-2020-fellows/
9/19 – current	Mellon Mays Undergraduate Fellows Travel and Research Grant, Woodrow Wilson National Fellowship Foundation ($5,000)
6/18 – 8/18	Predoctoral Research Dissertation Grant, Andrew W. Mellon Foundation ($3,000)
6/18 – 8/18	Graduate Student Enhancement Grant, Andrew W. Mellon Foundation ($687)
6/17 – 8/17	Graduate Student Enhancement Grant, Andrew W. Mellon Foundation ($1,350)

Internal Grants

3/20 – current	Global Health Catalyzer Research Fund, Institute for Global Health, Feinberg School of Medicine, Northwestern University ($25,000)
6/19 – 6/20	Morris Goodman Award for African Language Study (isiZulu), Program of African Studies, Northwestern University ($3,000)
3/19 – 3/20	Graduate Research Grant, The Graduate School, Northwestern University ($3,000)
6/18 – 8/18	Friends of Anthropology-Foster Award, Department of Anthropology, Northwestern University ($500)
6/18 – 9/18	Graduate Student Dissertation Research Travel Award, Buffett Institute for Global Studies, Northwestern University ($5,000)
6/18 – 9/18	Hans E. Panofsky Pre-Dissertation Research Award, Program of African Studies, Northwestern University ($2,000)
6/17 – 8/17	Graduate Student Dissertation Research Travel Award, Buffett Institute for Global Studies, Northwestern University ($4,877)
6/17 – 8/17	Friends of Anthropology-Foster Award, Department of Anthropology, Northwestern University ($700)
4/14 - 12/14	Independent Research Grant, Scholarly Inquiry and Research at Emory, Emory University ($2,500)
3/14 – 8/14	Independent Field Scholar Award, Emory Global Health Institute, Emory University ($3,000)

Publications

1. **Kim, A.W.**, Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. *Psychological Medicine.*

2. McKerracher, L., Fried, R., **Kim, A.W.**, Moffat, T., Sloboda, D. Galloway, T. (2020). Digest: Synergies between the Developmental Origins of Health and Disease (DOHaD) Framework and Multiple Branches of Evolutionary Anthropology. *Evolutionary Anthropology.*

3. Lambert, M., Mendenhall, E.M., **Kim, A.W.**, Cubasch, H., Joffe, M., Norris, S.A. (2020). Health System Experiences of Breast Cancer Survivors in urban South Africa. *Women's Health.*

4. **Kim, A.W.**, Adam, E.K., Bechayda, S.A., Kuzawa, C.W. (2020). Early life exposure to domestic violence and HPA axis function independently predict adult depression in metropolitan Cebu, Philippines. *American Journal of Physical Anthropology.*

5. Subramaney, U., **Kim, A.W.**, Chetty, I., Chetty, S., Jayrajh, P., Govender, M., Maharaj, P., Pak, E. Coronavirus Disease 2019 (COVID-19) and Psychopathology in South Africa: Anxiety and Beyond. *Wits Journal of Clinical Medicine.*

6. Mendenhall, E., Bosire, E., **Kim, A.W.**, Norris, S.A. (2019). Cancer, chemotherapy, and HIV: Living with Cancer amidst Comorbidity in a South African Township. *Social Science & Medicine.*

7. **Kim. A.W.**, Kaiser, B., Bosire, E., Shahbazian, K., Norris, S., Mendenhall E. (2019). Idioms of Resilience among Cancer Patients in Urban South Africa: An Anthropological Heuristic for the Study of Culture and Resilience. *Transcultural Psychiatry.*

8. Shreckengost, C. H., **Kim, A.W.**, Whitaker, S.H., Weng, L., Pearce, B.D., Kaiser, B.N. (2019). Prevalence of Folate Deficiency in Adult Men and Women in the Haitian Central Plateau. *International Health.*

9. Mendenhall, E., **Kim, A.W**. (2019). How to Fail a Scale: Reflections on a Failed Attempt to Assess Resilience. *Culture, Medicine, and Psychiatry.*
10. Thayer, Z.M., Wilson, M.A., **Kim, A.W**., & Jaeggi, A.V. (2018). Impact of prenatal stress on offspring glucocorticoid levels: A phylogenetic meta-analysis across 14 vertebrate species. *Scientific Reports*, 8(1), 4942.

Works in Progress

1. (Revise & Resubmit) **Kim, A.W.**, Lambert, M., Norris, S.A. Mendenhall, E. Barriers to treatment and social experiences of prostate cancer treatment among black South African men in Soweto, South Africa. *Global Public Health.*
2. (Revise & Resubmit) Ware, L.J., **Kim, A.W.**, Prioreschi, A., Nyati, L., Draper, C., Lye, S.J., Norris, S.A. Social vulnerability and parity in urban African young women: A Healthy Life Trajectories Initiative (HeLTI). *Journal for Public Health Policy.*
3. (Revise & Resubmit) **Kim, A.W.**, Mohamed, R.S., Kuzawa, C.K., Norris, S.A. (2020). Maternal prenatal stress during the first trimester and infant birthweight in Soweto, South Africa. *American Journal of Physical Anthropology.*
4. (Revise & Resubmit) Backe, E.L., Bosire, E.N., **Kim, A.W.,** Mendenhall, E. "Thinking Too Much": A Systematic Review of the Idiom of Distress in sub-Saharan Africa. *Culture, Medicine and Psychiatry.*
5. (Revise & Resubmit) Mpondo, F., **Kim, A.W.**, Tsai, A., Norris, S.A., Mendenhall, E. Psychometric Analyses of a Stress Checklist for Adults living in Soweto, South Africa. *Social Science & Medicine.*
6. (Submitted) **Kim, A.W.**, Burgess, R., Kwinda, Z., Chiwandire, N., Mendenhall, E. (2020). Perceptions, understandings, and impacts of the COVID-19 pandemic in urban South Africa.
7. (Submitted) Austin, M.K., White, I.I., Sodipe, A. **Kim, A.W.** Parental Incarceration and Child Physical Health Outcomes from Infancy to Adulthood: A Multi-Level Model of Potential Pathways and Critical Review.
8. (Submitted) Kolkenbeck-Ruh, A., Soepnel, L., **Kim, A.W.**, Naidoo, S., Smith, W., Davies, J., Ware, L.J. Pulse wave velocity in South African women and children: Comparison between the Mobil-O-Graph and SphygmoCor Xcel devices.
9. (Submitted) Mpondo, F., **Kim, A.W.**, Mendenhall, E., Tsai, A., Norris, S.A. Validation of a Social Coping Scale among Black South African adults in urban South Africa.
10. Murphy, R. & **Kim, A.W.** et al. Assessing healthcare capacity and early COVID-19 mitigation efforts in sub-Saharan Africa.
11. **Kim, A.W.**, Mohamed, R.S., Norris, S.A., Richter, L.M., Kuzawa, C.W. Psychological Legacies of Intergenerational Trauma under South African Apartheid: Prenatal Stress Predicts Increased Psychiatric Morbidity during Late Adolescence and Early Adulthood in Soweto, South Africa.
12. **Kim, A.W**., Tsai, A., Norris, S.A. Adverse childhood experiences predict adult psychiatric risk in Soweto, South Africa: developmental origins of psychopathology.
13. **Kim. A.W.**, Ryan, C.P., McDade, T.W., Borja, J., Kuzawa, C.W. Childhood exposure to domestic violence does not affect adult depression through DNA methylation.
14. **Kim, A.W.**, Mohamed, R.S., Kuzawa, C.W., Norris, S.A. Examining the effects of antenatal stress exposure among black South African women during apartheid on late adolescent inflammation in Soweto, South Africa.

15. **Kim, A.W.**, Vrshek-Schallhorn, S., Adam, E.K. Genetic polymorphisms of HPA axis function, chronic and recent stress, and diurnal cortisol rhythms.
16. **Kim, A.W.**, Bosire, E., Norris, S.A. Mendenhall, E. Idioms of distress and ethnophysiological models of stress, resilience, and illness in Soweto, South Africa.

Short reports, editorials, and commentaries

1. **Kim, A.W.** (2020). Promoting mental health in community and research settings during COVID-19: Perspectives and experiences from a South African epidemiological study. Invited Commentary. *American Journal of Human Biology*.
2. **Kim. A.W.** (2020). Is it time to rethink how we deliver mental healthcare services? *Mental Health Matters*. 7(3), 30-32.
3. **Kim, A.W.** (2020). How should we study intergenerational trauma? Reflections from a 30-year birth cohort study in Soweto, South Africa. *Somatosphere*.

Book chapters

1. (In press) **Kim, A.W.**, Subramaney, U. Psychiatric Morbidity and Mental Healthcare during the Coronavirus Pandemics in South Africa. In *Dhai, A., Ballot, D. Veller, M.* (Eds.) *Pandemics in Healthcare: Principles, Processes and Practice.* Cape Town: JUTA Academic.
2. (In press) Mendenhall, E., **Kim, A.W.**, Bosire, E. (2020). Qualitative Research in Mental Health in the African Context. In *Ndetei, D.* (Eds.) *African Textbook of Clinical Psychiatry and Mental Health.* Second Edition. Nairobi: The African Medical and Research Foundation.
3. (In press) Mendenhall, E., **Kim, A.W.** (2020). Rethinking Idioms of Distress and Resilience in Anthropology and Global Mental Health. In Dyer, A., Kohrt, B., Candilis, P., & Cratsley, K. (Eds.) *Textbook of Global Mental Health: Ethical Principles and Best Practices.* New York: Springer.
4. Smith, A.K., Parets, S.E., **Kim, A.W.** (2013). Epigenetics of Psychopathology. In Rhee, S.H. & Ronald, A. (Eds.), *Behavior Genetics of Psychopathology*. New York: Springer.

Reports, Public Articles, and Other Publications

1. **Kim. A.W.,** Mendenhall. E. Mental health and childhood trauma influenced how people perceived risk for COVID-19 during the first six weeks of South African lockdown. *The Conversation.* https://theconversation.com/people-in-soweto-told-us-about-their-fears-in-the-first-weeks-of-south-africas-lockdown-142325
2. **Kim. A.W.** COVID-19 has changed the way South Africa's only toll-free mental health hotline works. Here's why it matters. 8 August 2020. *Bhekisisa Centre for Health Journalism.* https://bhekisisa.org/article/2020-08-11-covid19-mental-health-south-africa-telemedicine-depression-anxiety-group/
3. **Kim. A.W.** (2020). Co-creating an integrated approach to Mental Health/Psychosocial Support Services & Peacebuilding – Preliminary findings. Institute for Justice and Reconciliation. January 2020.
4. **Kim. A.W.** (2016). Community food assessment in La Alma-Lincoln Park. Hunger Free Colorado. Congressional Hunger Center. February 2016.
5. **Kim. A.W.** (2016). Food insecurity in farmworker communities. Farmworker Justice. Congressional Hunger Center. August 2016.

Professional Presentations with Published Abstracts

1. **Kim, A.W.**, Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. 2020 African Studies Association Annual Meeting.
2. Burgess, R., **Kim, A.W.**, Hagaman, A. Protecting and promoting mental health among research teams in public health research: context, practices, and recommendations. Interdisciplinary Association for Population Health Science. 1 October 2020.
3. **Kim, A.W.**, Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. 2020 COVID-19 Conference - International AIDS Society. 10 July 2020.
4. **Kim, A.W.**, Mendenhall, E. (2019). Approaches to the Prevention of Diabetes in Low- and Middle-Income Contexts: Rethinking Diabetes through a Syndemic Framework. 2019 International Diabetes Federation Congress. Busan, South Korea. 5 December 2019.
5. **Kim, A.W.** (2019). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. Social Science Research Council-Mellon Mays Summer Conference. Environmental Stressors. 19 June 2019.
6. **Kim, A.W.**, Mohamed, R.S., Nyati, L., Kuzawa, C.K., Norris, S.A. Evaluating the effects of maternal prenatal stress on fetal growth patterns and birth outcomes in Soweto, South Africa. 2019 American Association of Physical Anthropologists meetings.
7. **Kim, A.W.**, Ngwepe, P.D., Chirwa, T., Mohamed, R.S., Kuzawa, C.W., Norris, S.A. Evaluating the long-term impacts of prenatal stress from apartheid on adult inflammation, blood pressure, and mental health risk in Soweto, South Africa. 2019 Human Biology Association meetings.
8. **Kim, A.W.**, Ryan, C.P., Bechayda, S.A, McDade, T.W., Kuzawa, C.W. Early life social experiences as predictors of depression in Cebu, Philippines: Investigating the mediating roles of the HPA axis and DNA methylation. Developmental Origins of Disease: Biocultural and Evolutionary Insights from Working with Vulnerable Human and Non-Human Populations. 2018 Canadian Association for Physical Anthropology meetings.
9. **Kim, A.W.**, Ryan, C.P., Borja, J., McDade, T.W., Kuzawa, C.W. (2018). Early life social experiences as predictors of depression in Cebu, Philippines: Investigating the mediating roles of the HPA axis and DNA methylation. 2018 Human Biology Association meetings.
10. **Kim, A.W.** (2018). Evaluating Resilience in Urban South Africa: Mixed Methods Perspectives on Psychometrics. 2017 Society for Applied Anthropology. Paper in panel titled "Measuring mental health and resilience across cultures: reflections on mixed-methods approaches to scale development and adaptation." Panel organizer.
11. **Kim, A.W.**, Borja, J., Kuzawa, C. (2018). Early life exposure to domestic violence and HPA axis function independently predict adult depression in metropolitan Cebu, Philippines. Department of Anthropology Prospective Students Symposium, Northwestern University.
12. **Kim, A.W.**, McDade, T., Borja, J., Kuzawa, C. (2017). Evaluating the social buffering effects of social support on the HPA axis and depressive symptoms in Cebu City, Philippines. 2017 American Anthropological Association meetings.

13. **Kim, A.W.**, Smith, A., Wingo, A., Kilaru, V., Ressler, K. (2017). Methylation of *SNAPC1* is related to resilience in a highly-traumatized Black Sample. 2017 Human Biology Association.
14. Kim, Y-K., **Kim, A.W.**, Tiemeyer, T. (2011). GxE interaction on *Drosophila* aggressive behavior. 2009 Behavior Genetics Association Annual Meeting. Minneapolis, Minnesota.
15. Kim, Y. K., Kim, A., & Tiemeyer, M. (2009). Social experience modulates Drosophila behavior and brain function. Behavior Genetics, 39(6).

Professional Presentations with Published Abstracts

1. **Kim. A.W.,** Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. Department of Psychiatry, University of the Witwatersrand. Johannesburg, South Africa. 21 October 2020.
2. **Kim. A.W.,** Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. Pharmaceutical & Technology Clinical Management Association. Johannesburg, South Africa. 14 October 2020.
3. **Kim. A.W.,** Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. Johannesburg Health District. Johannesburg, South Africa. 2 September 2020.
4. **Kim. A.W.,** Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. South African Depression and Anxiety Group Counsellors' Training. South African Depression and Anxiety Group. Johannesburg, South Africa. 7 August 2020.
5. **Kim. A.W.,** Nyengerai, T., Mendenhall, E. (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. Internal Seminar. Health Economics and Epidemiology Research Office (HE2RO), University of the Witwatersrand. Johannesburg, South Africa. 18 February 2020.
6. **Kim. A.W.** (2019). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. Internal Seminar. Health Economics and Epidemiology Research Office (HE2RO), University of the Witwatersrand. Johannesburg, South Africa. 18 February 2020.
7. **Kim. A.W.** (2019). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. Internal Seminar. National Center for Global Health and Medicine. Tokyo, Japan. 16 December 2019.
8. **Kim. A.W.** (2019). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. Internal Seminar. Historical Trauma and Transformation Unit, Stellenbosch University. Stellenbosch, South Africa. 27 November 2019.
9. **Kim, A.W.** (2019). The Biology of Trauma. South African Depression and Anxiety Group Counsellors' Training. South African Depression and Anxiety Group. Johannesburg, South Africa. 26 October 2019.
10. **Kim, A.W.** (2019). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto,

South Africa. Internal Seminar. Center for the Study on Violence and Reconciliation. Johannesburg, South Africa. 15 October 2019.

11. **Kim, A.W.** (2018). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. Human Development Lab Brown Bag Series, School of Education and Social Policy, Northwestern University. 10 May 2019.
12. **Kim, A.W.** (2018). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. AfriSem, Program of African Studies, Northwestern University. 18 April 2019.
13. **Kim, A.W.**, Ryan, C.P., Borja, J., McDade, T.W., Kuzawa, C.W. (2018). Early life social experiences as predictors of depression in Cebu, Philippines: Investigating the mediating roles of the HPA axis and DNA methylation. Population Health Forum/Global Health Day, Northwestern University Institute for Public Health and Medicine, 4 December 2018.
14. **Kim, A.W.** (2018). Biological memories of apartheid: Evaluating the intergenerational effects of apartheid-based prenatal stress on birth outcomes, HPA axis function, and mental health in Soweto, South Africa. Prospectus defense. Department of Anthropology, Northwestern University. 26 October 2018.
15. **Kim, A.W.**, Ryan, C.P., Borja, J., McDade, T.W., Kuzawa, C.W. (2018). Early life social experiences as predictors of depression in Cebu, Philippines: Investigating the mediating roles of the HPA axis and DNA methylation. Developmental Pathways for Health Research Unit Postgraduate Journal Club, Soweto, South Africa, 7 August 2018.
16. **Andrew W. Kim**, Varun Kilaru, Karen N. Conneely, Elisabeth B. Binder, Sasha E. Parets, Kerry J. Ressler, Alicia K. Smith, "Tobacco smoking-related DNA methylation patterns: A replication study," Creativity in the Arts & Sciences Event – HHMI-UF Science for Life, Gainesville, FL, January 2013.
17. **Kim, A.W**, Kim, Y-K., Anderson, W.A. "Epigenetic interactions influence *Drosophila* brain function and aggressive behavior," Creativity in the Arts & Sciences Event – HHMI-UF Science for Life, Gainesville, FL, 22 January 2012.
18. **Kim, A.W**, Kim, Y-K, Anderson, W.A, "Gene x Environmental interactions influence *Drosophila* brain function and aggressive behavior," Stockholm International Youth Science Seminar, 2011 Nobel Prize Ceremony, Stockholm, Sweden, 7 December 2011.
19. **Kim, A.W**, Kilaru, V., Conneely, K.N., Binder, E. B., Parets, S.E., Ressler, K.J., Smith, A.K. "Tobacco smoking-related DNA methylation patterns: A replication study," Scholarly Inquiry and Research at Emory Undergraduate Research Symposium, Atlanta, GA, 24 April 2012.
20. **Kim, A.W**, Kim, Y-K, Anderson, W.A, "Gene x Environmental interactions influence *Drosophila* brain function and aggressive behavior," 2011 Intel International Science and Engineering Fair, Society for Science & the Public, Los Angeles, CA, 14 May 2011
21. **Kim, A.W**, Kim, Y-K, Anderson, W.A, "Social experience modulates *Drosophila* aggressive behavior," 2010 Intel International Science and Engineering Fair, Society for Science & the Public, San Jose, CA, 7 May 2010

Teaching experience

1. Teaching assistant to Dr. Thomas McDade, Northwestern University, Evanston, IL, Spring 2019, "Social and Health Inequalities" – ANTHRO221

2. Teaching assistant to Dr. Peter Locke, Northwestern University, Evanston, IL, Winter 2019, "Introduction to International Public Health" – GH310 (two weekly 50-minute sections)
3. Teaching assistant to Dr. Christopher Kuzawa, Northwestern University, Evanston, IL, Fall 2018, "Evolutionary Medicine" – ANTH390
4. Co-teacher, Freedom University, Atlanta, GA, Fall 2013-Spring 2015, SAT and college preparation classes
5. Teaching assistant to Hilary King and Dr. Peggy Barlett, Emory University, Atlanta, GA, Fall 2013, "Sustainable Food Fair" – ANT386
6. Instructor, Emory University, Atlanta, GA, Fall 2012, "It's Your Health" – HLTH100

Guest lectures

1. Guest lecture, Promises & Perils: The Social Reality of Biology, Dr. Marcelo Vinces, Program of Biological Sciences, Northwestern University, 19 October 2020.
2. Guest lecture, The Politics of Health Crises: The Life Healthcare Esidimeni Tragedy, Dr. Lorena Nuñez Carrasco, "The Sociology of Health and Illness", University of the Witwatersrand, 14 May 2020.
3. Guest lecture, Theorizing Culture and Mental Health, Dr. Lorena Nuñez Carrasco, "The Sociology of Health and Illness", University of the Witwatersrand, 2 April 2020.
4. Guest lecture, Promises & Perils: The Social Reality of Biology, Dr. Marcelo Vinces, Program of Biological Sciences, Northwestern University, 17 May 2019.

Mentorship

Research lead, South African Depression and Anxiety Group Research Group. (August 2019-March 2021).

- Organized needs assessment of mental health and healthcare among adults in Gauteng Province before and during the COVID-19 pandemic
- Coordinated evaluation of 24/7 counselling call center through qualitative research
- Led weekly trainings, meetings, and activities with research volunteers applying for Master's and PhD programs

Organizer, "Navigating the application process and graduate school experiences," Panel discussion for Mellon Mays Undergraduate Fellows at Northwestern University. 25 April 2018.

Graduate mentor for undergraduate thesis, Jennah Thompson-Vazquez, biological anthropology undergraduate student (2016-2017)

- Mellon Mays Undergraduate Fellow, Northwestern University

Graduate mentor for undergraduate thesis, De'Sean Weber, cultural anthropology undergraduate student (2016-2017)

- Oswald Werner Prize for Distinguished Honors Thesis in Anthropology awardee
- Emerson National Hunger Fellow, Congressional Hunger Center

Research experience

Department of Anthropology, Northwestern University, Dr. Chris Kuzawa & Dr. Shane Norris

- Studying the biological mechanisms and intergenerational effects of apartheid-based stress and trauma on physical and mental health in Soweto, South Africa
- Evaluating the impacts of prenatal stress on fetal growth trajectories and birth outcomes from a life-history perspective

Developmental Pathways for Health Research Unit, Dr. Emily Mendenhall & Dr. Shane Norris

- Studying the social experience of co-morbidities among patients at Chris Hani Baragwanath Hospital in Soweto, South Africa
- Examining "idioms of resilience" among co-morbid cancer patients

Farmworker Justice, Congressional Hunger Center

- Published white paper on food insecurity in farmworker communities nationwide
- Wrote memos, blogs, and tracked media updates for policy advocacy

Hunger Free Colorado, Congressional Hunger Center

- Conducted community food assessment to understand hunger and food insecurity and provide recommendations to improve food security in the La Alma-Lincoln Park neighborhood of Denver, Colorado
- Conducted surveys, interviews, focus groups, and literature reviews to identify availability of, barriers to, and utilization of food; coping mechanisms; and community-based solutions to addressing hunger and food insecurity

Violence Against Children Study, Centers for Disease Control and Prevention, Drs. Howard Kress and James Mercy

- Conducted literature reviews on best methods to quantify food insecurity and its effects on violence and mental health, and household economic status in low- and middle-income countries

Department of Anthropology, Emory University, Drs. Craig Hadley and Bonnie Kaiser

- Conducted research on the risk and protective factors affecting mental illness in rural Haiti
- Summer field research collecting and analyzing survey data and biomarkers in Mirebalais, Haiti
- Enrolled in intensive Haitian Creole language course for four months
- Presented research findings at the Emory SIRE research symposium; received 2nd place best presenter award

Hubert Department of Global Health, Rollins School of Public Health, Emory University Dr. Juan Leon

- Created surveys in Spanish to study the nutritional and immunological factors of the rotavirus in Bolivia
- Entered and analyzed data from surveys to create recommendations for future directions
- Managed visiting Brazilian medical students in researching and drafting policy briefs for the Brazilian Ministry of Health

Yerkes Primate Research Center, Behavioral Neuroscience and Psychiatric Disorders, Emory School of Medicine, Dr. Larry Young

- Studied the natural genotypic variation of the oxytocin receptor and its role on pair-bonding and parenting behavior in prairie voles

Grady Trauma Project, Department of Psychiatry and Behavioral Sciences, Emory School of Medicine-Grady Memorial Hospital & Atlanta Veterans Affairs Medical Center, Dr. Kerry Ressler, Dr. Alicia Smith, Dr. Aliza Wingo

- Conducted extensive psychological screens on patients to study the genetic-environmental factors that affect PTSD in the inner-city Atlanta population
- Created multivariate models to study the effects of child abuse on adult resilience and mediating effect of methylation

Department of Clinical Pharmacy, University of Georgia, Drs. Brad Phillips & Rob Meagher

- Designed a protocol to preserve DNA profile of CD4+ white blood cells in frozen whole blood samples

Laboratory of Psychiatric Genetics and Epigenetics, Department of Psychiatry and Behavioral Sciences, Emory School of Medicine, Dr. Alicia Smith

- Conducted research on epigenetic profile of smokers and the mentally-ill
- Co-authored a chapter on the Epigenetics of Psychopathology
- Presented research findings at the Emory SIRE research symposium; nominated for best presenter in the Natural Sciences category

Department of Genetics, University of Georgia, Dr. Wyatt Anderson

- Conducted independent research on the gene x environment (GxE) factors that influence Drosophila aggressive behavior and brain function

Department of Biochemistry and Molecular Biology, Complex Carbohydrate Research Center, University of Georgia, Dr. Michael Pierce

- Studied the role of glycosyltransferases (GnT-Va) and galectins on prostate cancer cell-cell adhesion and metastasis

Consulting

Evaluator, South African Depression and Anxiety Group, September 2020
Qualitative Researcher, Chicago Youth Ideas Festival, October 2018

Service

Ad hoc peer reviewer: Annals of Human Biology (2), BMC Psychiatry (4), European Journal of Psychotraumatology, JMIR Cancer, Medical Anthropology Quarterly, Psychitria Danubina (2), Psychoneuroendocrinology (2), Social and Health Sciences, Social Science & Medicine (3), Journal of the International AIDS Society

Chair, Diversity Committee, Department of Anthropology, Northwestern University, Fall 2016-Spring 2017

Co-founder, Freedom at Emory University

- Led coalition of student organizations, alumni groups, academic departments, and community organizations to amend admissions and financial aid policies to provide need-based financial aid for undocumented students at Emory University.

Media Coverage

1. **Scientific American – Arabic Version**. https://www.scientificamerican.com/arabic/articles/news/warnings-about-danger-of-covid-19-on-mental-health/. 11 November 2020. Article.
2. **Health24.** Lockdown, pandemic effects: Soweto study re-emphasises need for better access to mental healthcare. https://www.health24.com/medical/infectious-diseases/coronavirus/lockdown-pandemic-effects-soweto-study-re-emphasises-need-for-better-access-to-mental-healthcare-20201027-3.
3. **Cambridge University Press.** Fear of COVID-19 raises risk of depression among Soweto's deprived communities. Press Release. Syndicated in *Healio*, *Medical Xpress*

4. **The Lancet Digital Health.** Africa turns to telemedicine to close mental health gap. 1 November 2020. News article. https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30252-1/fulltext#%20.
5. **Radio 702 – Afternoon Drive with Joanne Joseph.** COVID-19 has changed the way SA's only toll-free mental health helpline works. Here's why it matters. 11 August 2020. Radio interview. https://www.702.co.za/podcasts/196/the-best-of-afternoon-drive-with-joanne-joseph/349175/covid-19-has-changed-the-way-sas-only-toll-free-mental-health-helpline-works-heres-why-it-matters.
6. **Bhekisisa Centre for Health Journalism.** COVID-19 has changed the way South Africa's only toll-free mental health helpline works. Here's why it matters. 11 August 2020. Opinion article. https://bhekisisa.org/article/2020-08-11-covid19-mental-health-south-africa-telemedicine-depression-anxiety-group/. Syndicated in *The Daily Maverick*.
7. **GauTV – Daughters of Destiny.** Biology of Gender-Based Violence. 1 November 2019.
8. **ScienceDaily.** Humans and others exposed to prenatal stress have high stress levels after birth. 10 April 2018. https://www.sciencedaily.com/releases/2018/04/180410161135.htm
9. **The Atlanta Journal Constitution.** Emory to help immigrant students. 18 April 2015. http://www.ajc.com/news/local-education/emory-help-immigrant-students/YuPLJyycdVhzQtBY8dHalJ/
10. **WABE - NPR's Local Atlanta Radio Station**. Emory To Offer Financial Aid To Some Undocumented Students. 3 April 2015. https://www.wabe.org/emory-offer-financial-aid-some-undocumented-students/

Professional Associations

Human Biology Association
Society for Applied Anthropology
American Anthropological Association
Society for Psychological Anthropology
Society for Research in Child Development

Skills

Language: Spanish (intermediate), Korean (intermediate), isiZulu (beginner), Haitian Kreyòl (beginner)
Statistical packages: Stata, R, HLM7, Dedoose, Excel

References

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