DISSERTATION

BIOMARKERS OF ALLOSTATIC LOAD MEDIATE STRESS AND DISEASE: A PROSPECTIVE STRUCTURAL EQUATION MODEL

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ABSTRACT

BIOMARKERS OF ALLOSTATIC LOAD MEDIATE STRESS AND DISEASE: A PROSPECTIVE STRUCTURAL EQUATION MODEL

Minority stress theory is often cited as the explanation behind physical health disparities for sexual minority individuals, but the exact mechanism linking a stigmatizing social environment to outcomes of disease is not well understood. This study sought to bridge minority stress theory with the theory of allostatic load in physiology. A sequential mediation model was hypothesized, in which sexual orientation would predict higher rates of cancer, cardiovascular disease, and more chronic conditions, mediated via two intervening variables: everyday discrimination and allostatic load. Using data from the MIDUS, $N = 495$ participants ($n = 45$ sexual minority) were followed prospectively from 1995 -2015. No differences by sexual orientation were found for cancer or cardiovascular disease. Being a sexual minority, experiencing more everyday discrimination, and having a higher allostatic load score were all significantly associated with having a greater number of chronic conditions. Mediation and the indirect effect were not fully supported. This study was an important first step in beginning to identify the causal pathways that link sexual minority stress to disease. Further research that uses more comprehensive measures of multi-dimensional minority stress, and/ or that consider alternative operationalizations of physiological functioning are needed to better elucidate the exact process.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Scientific research on the health and well-being of sexual minority populations has come a long way in the past 50 years, but it has stalled again recently. The forward momentum began as early as the 1970s when the Diagnostic and Statistical Manual of Mental Disorders officially eliminated homosexuality as a mental disorder from the book's second edition printing (DSM-II, 1973). Researchers then spent most of the 1990s and early 2000s trying to articulate that while being homosexual isn't itself inherently pathological, sexual minorities do carry a higher prevalence of mental health issues than does the general population (e.g. Fergusson et al., 1999; Cochran & Mays, 2000; Gilman et al., 2001; Sandfort et al., 2001). Meyer (1995; 2003) then changed the entire discourse of the field by providing a theoretical framework in which to ground these issues- positing that it is not the dysfunction of the individual, but rather the stressful social environment they are exposed to that causes mental health disorders.

From there, experts on sexual minority health made another leap- hypothesizing that these disparities may extend to physical health issues as well, and they were correct (Cochran & Mays, 2007). Over the past ten years, descriptive evidence has been accumulating to document that such physical health disparities do exist. The vast majority of such published studies refer back to Meyer's (1995; 2003) theoretical model to explain what the driving force is behind the disparities between sexual minority and heterosexual populations, leading to a stall in research progress. The existing body of literature asks the reader to make a significant logical leap from "sexual minority individuals live in a highly stressful social environment" to "living in a stressful social environment causes physical health problems" without establishing what happens in between. Hatzenbuehler (2009) extended Meyer's (1995; 2003) minority stress theory to explain

the actual cognitive processes that happen between, say, being called a slur and experiencing a major depressive episode. He argues that cognitive processes such as emotion dysregulation, maladaptive coping motives, rumination, negative self-schemas, and social isolation mediate the relationship between minority stress and psychopathology (Hatzenbuehler, 2009). This theoretical extension of Meyer's (1995; 2003) model has not yet occurred for physical health outcomes. That is the purpose of this dissertation: to propose a mechanism for what is happening between step A and step B.

Physical Health Disparities

Before launching into the meat of my central thesis, I will first give an overview of what are the physical health disparities that need explaining. Sexual minority individuals are overrepresented in many of the chronic conditions that make up the leading causes of death in the United States. For example, the number one leading cause of death is cardiovascular disease (CDC, 2017). Numerous studies have reported that sexual minority individuals have higher rates of or are at greater risk for cardiovascular disease compared to heterosexual individuals (Boehmer, Miao, Linkletter, & Clark, 2014; Diamont & Wold, 2003; Roberts, Dibble, Nussey, & Casey, 2003; Case et al., 2004; Conron, Mimiaga, & Landers, 2010).

Sexual minority individuals also experience higher rates of several different types of cancer (Boehmer et al., 2014; McNair, Szalacha, & Hughes, 2011), the second leading cause of death (CDC, 2017). Specific types of cancer identified include non-Hodgkin's lymphoma (Koblin et al., 1996), anal cancer (Koblin et al., 1996), and breast cancer (Meads & Moore, 2013; Kavanaugh-Lynch, White, Daling, & Bowen, 2002; Case et al., 2004; Dibble, Roberts, & Nussey, 2004; Brandenburg, Matthews, Johnson, & Hughes, 2007).

Chronic lower respiratory diseases, of which asthma is an example, make up the fourth leading cause of death (CDC, 2017). Asthma has been found to disproportionately burden the sexual minority population in a number of studies (Blosnich, Farmer, Lee, Silenzio, & Bowen, 2014; Heck & Jacobson, 2006; Dilley, Simmons, Boysun, Pizacani, & Stark, 2010; Conron et al., 2010; Landers, Mimiaga, & Conron, 2011; McNair et al., 2011; Fredriksen-Goldsen et al., 2012; Kim & Fredriksen-Goldsen, 2012). Differences by sexual orientation have also been found for diabetes, the 7th leading cause of death in the United States (Dilley et al., 2010; Wallace, Cochran, Durazo, & Ford, 2011). Other disparities include obesity for women only (Eliason et al., 2015), hypertension, high cholesterol, arthritis, and worse self-reported health/ functioning (see Simoni, Smith, Oost, Lehavot, & Fredriksen-Goldsen, 2017; Lick, Durso, & Johnson, 2013 for reviews.)

Differential Diagnosis

One explanation that has been put forth to understand the source of such health disparities is structural stigma. Structural stigma is the idea that institutions engage in systemic discrimination that creates barriers to accessing health care. Past research reported that individuals struggled to get health insurance under their same sex partner's plan (Cochran et al., 2001) but more recent studies have shown that sexual minority individuals are actually more likely to be insured than heterosexuals (Boehmer et al., 2012; Caceres et al., 2018). That change could be attributable to changes in legislation over that time period; individual states began legalizing same-sex marriage in 2004 up until the Supreme Court overturned the Defense of Marriage Act in 2015.

Regarding utilization of healthcare services, several studies have found that sexual minority women are more likely to avoid medical care, such as physical or dental exams, due to

cost compared to heterosexual women. Studies have not found those differences for men (Strutz, Herring, & Tucker Halpern, 2015; Blosnich et al., 2014). Even taking that into account, two studies found no difference in breast cancer screening for sexual minority vs. heterosexual women, and yet they still found the sexual minority women were at higher risk for developing cancer (Brandenburg et al., 2007; Dibble et al., 2004). In contrast, Boehmer et al. (2012) reported that sexual minority were more likely to have been screened for colon cancer than heterosexual men.

Another barrier to accessing health care is that sexual minority people often don't feel safe going to the doctor, for fear they will be treated unkindly (Petroll & Mosack, 2011). In a recent systematic review, the key themes the authors distilled from the literature were that sexual minorities avoided going to the doctor until it was severe enough for the ER, and that they had difficulty accessing the correct services for their sexual health needs because of prejudice (Alencar Alberquerque et al., 2016). While barriers to healthcare may contribute to sexual minority health disparities, it is unlikely to be the sole driving factor.

A secondary explanation that has been posited for these widespread disparities is that sexual minorities have greater behavioral risk factors (presumably due to maladaptive coping/ poor lifestyle choices.) This hypothesis is only partially supported. Sexual minority individuals do consistently report more behavioral risk factors than do heterosexuals. They are much more likely to use tobacco (Lee, Griffin, & Melvin, 2009) and report more alcohol use and binge drinking (Corliss, Rosario, Wypij, Fisher, & Austin, 2008). A meta-analysis showed that sexual minorities are anywhere from two to five times more likely to abuse substances than heterosexuals (Marshal et al., 2008). The minority group is less likely to exercise (Calzo et al., 2014; Mereish & Poteat, 2015) and tends to eat a poorer diet (Boehmer & Bowen, 2009).

However, it is considered standard practice to control for as many of these factors as feasible in any kind of health research. Indeed, in the majority of the studies summarized in my following literature review, the behavioral risk factors somewhat attenuated the relationship between sexual orientation and health outcomes, but did not fully eliminate it. That is, across numerous studies, the relationship between sexual orientation and health outcomes remains statistically significant even after adjusting for behavioral risk factor covariates. With that in mind, there must be some other unaccounted-for factor driving the disparities.

Theoretical Framework

To begin answering that question, I will draw on two theoretical frameworks from two different academic fields. The first framework comes from social psychology. It is the sexual minority stress model I referenced earlier (Meyer 1995; 2003). I have chosen this model because it is most directly relevant to the population of study for my dissertation, however it should be noted that many other social scientists too have separately proposed similar theories to explain the link between social stigma and poor health/ functioning. For example, Geronimus's (1992) weathering hypothesis has been used to explain why young black women's health declines earlier than white women's health. Another similar theoretical explanation for disparate racial minority health is Clark, Anderson, Clark, and Williams's (1999) biopsychosocial model, which states that repeated exposure to racist events leads to poor health outcomes. Greene's (1996) theory of triple jeopardy explains how having multiple minority statuses, such as race and gender, puts the individual at an even greater disadvantaged position. Crenshaw's (1995) intersectionality theory (an expansion of triple jeopardy) argues that having multiple stigmatized identities has a synergistic, interactive effect beyond the sum of the parts. Ultimately, social scientists have been iteratively attempting to articulate how a hostile social environment is linked

to worse off mental/ physical health for minority individuals. The Meyer (1995; 2003) model is really an amalgamation of all the groundwork laid by the researchers above, and fine-tuned to explain the particular nuances of sexual minority stressors.

To derive the theory, Meyer (2003) conducted a meta-analysis on all of the different studies published on LGB mental health, as that was the major focus of published work on sexual minority populations at the time. He then built his theoretical framework around explaining the clear and consistent trend the meta-analysis was showing: that sexual minority individuals have significantly worse health outcomes than heterosexual individuals. The model is broken out into two main branches- distal stressors and proximal stressors. These distinctions stem from Lazarus and Folkman's (1987) transactional theory of stress, which was among the first models to suggest that the stress/ health literature and the emotional coping literatures should be merged. The authors point out that an external stressor must be cognitively perceived as negative by the individual in order for it to cause them distress. This perception is the primary appraisal. From there, the individual will decide if she/he has any control to alter or influence the stressful thing in the environment. This is the secondary appraisal. The secondary appraisal then determines what kind of coping mechanism the individual uses. If the individual feels he/she has power to change the stressor- he/she will engage in problem-focused coping to take actions to eliminate the source of the stress. Simultaneously, the individual will also engage in emotion-focused coping to manage their arousal. The appraisals and the coping mechanisms then, are what determines what kind of long-term outcome the stressor will yield, be it physical illness and isolation or adjustment and well-being (Lazarus & Folkman, 1987).

Meyer (1995; 2003) simplified the transactional theory down to just distal and proximal stressors and has used that to explain how prejudice impacts the individual. He describes the

outward external stressors as distal conditions. These stressors include discrimination events (e.g., being denied a job) and victimization events (e.g., getting beaten up at a bar). Straddling the line between distal/ proximal are microaggressions- small everyday slights that happen in the external environment, but that the individual must perceive as offensive. Then, there are the individual's subjective internal responses to those events, which are stressors in and of themselves which are proximal stressors. Such secondary responses can include remaining in a state of hypervigilance to always scan for people/situations that might hurt you again (rejection anticipation). The secondary responses can also include concealing one's sexual minority status to prevent becoming a target (identity concealment), and may even include internalizing the negative attitudes that society holds and loathing oneself (internalized stigma).

It is easy to see how those minority stress processes contribute to poor mental health outcomes. Chronic hypervigilance and restlessness are defining symptoms of both generalized anxiety disorder and post-traumatic disorder, just as low self-esteem and feelings of worthlessness can be symptoms of major depressive disorder (ADAA, 2019). There are clear parallels between the minority stress features and the mental disorder symptoms (rejection anticipation and hypervigilance, internalized stigma and decreased self-esteem). What is less clear is how the minority stress processes cause physical problems, like plaque in the arteries or cancer. Indeed, Meyer (2003) does not address that matter in his seminal article, even though other scholars have frequently cited it as an explanation for disparate health outcomes. Nor do any of the other social science theories that preceded it articulate the precise biological mechanism that links stigma to physical health.

Therefore, the second major framework I will draw on to address this missing link is the theory of allostatic load. The theory was conceived of by a neurobiologist, Peter Sterling, and an

epidemiologist, Joseph Eyer (1988). Their most simple three-word definition of allostasis is, "stability through change" (Sterling & Eyer, 1988, pp. 5). Allostasis is a comprehensive model to explain how the body maintains itself, and how chronic stress wears down its ability to do that over time. Sterling and Eyer (1988) built out the model to challenge the existing paradigm found in just about all biology textbooks of the time: homeostasis. The theory of homeostasis dictates that there are ideal parameters for everything (e.g., your body temperature should always be 98.6 degrees, or your blood pressure should always be 120/80). Homeostasis treats each of those systems as independent. Any value outside of the pre-defined set-point is inherently abnormal and pathological, regardless of what the rest of the body is doing.

The allostasis paradigm is different than previous paradigms because it views the body as a dynamic, highly interdependent, and predictive organism (Sterling & Eyer, 1988). It is a good thing that the body operates outside of the perfect values for temperature and blood pressure sometimes, because this is how it adapts to the ever-changing demands we put on it, such as when exercising. Sterling and Eyer (1988) argue that the upside to a domino system is that it allows us to be predictive. If an individual knows they are going out for a night of binge drinking, they can predict all of the dominos that are going to fall in response to that (headache, fatigue), and add another push to the system to change how the dominos might fall (drink a lot of water, take aspirin). Sterling and Eyer (1988) describe this adaptability as a highly efficient feedback loop.

Of course, because it is a feedback loop, chronic stress can cause serious harm to the body that affects many interdependent systems (McEwen, 1998). For example, if your boss yells at you, the HPA axis secretes ACTH, signaling the sympathetic-adrenal-medullary system to release stress hormones: epinephrine, norepinephrine, and cortisol. Then, if you receive a passive

aggressive email, more stress hormones are released. These stressful experiences continue to build up over time. In acute stress situations, those stress hormones signal the release of anti-inflammatory cytokines, which turn off the body's immune system temporarily so that resources can be devoted to dealing with the immediate threat (i.e. enabling the fight or flight response). Likewise, under normal conditions, those stress hormones bind to their mineralocorticoid and glucocorticoid receptors, and once bound, are able to signal the HPA axis to shut off after the threat is eliminated (McEwen, 1998; Burrage, Marshall, Santanam, & Chantler, 2018)

When there are too many stress hormones constantly circulating through the body, as is the case with chronic daily stress, they interfere with the gene transcription process and decrease the amount of receptors in the brain (McEwen, 1998). When there are not enough receptors for the stress hormones to bind with, they are not able to transmit their signals to tell the HPA axis to stop the stress response or to tell the immune system it should turn off the inflammatory response. At this stage, the negative feedback loop has failed, and the stress response and inflammation are allowed to run rampant in the body (McEwen, 1998).

Another problem with excess stress hormones is that they can cause changes in the body that make it easier to innervate the SNS in the first place. In a review, Miller et al. (2009) argue that that by interfering with the transcription of certain genes, stress hormones can cause tissue to remodel itself in ways that leave it hypersensitized to stress. One example of this that the review cites is a study conducted by Sloan et al. (2007) in which the researchers put macaques in stressful living environments. The stressed animals were found to have a significantly higher density of catecholaminergic varicosities inside their lymph nodes compared to the not stress-exposed animals. Sloan et al. (2007) attribute that finding to differences in NGF gene expression between the stressed and unstressed primates. Miller et al. (2009) summarize the primary

evidence by explaining that when there are more neurons available to excite, it becomes easier for stressful stimuli to trigger the stress response and start the whole loop over again next time.

In the allostatic load model, corticosteroids (cortisol) and catecholamines (norepinephrine, and epinephrine) are the primary mediators of chronic health outcomes (McEwen, 2003). Once they start to run rampant, the metabolic, cardiovascular, and immune systems try their best to compensate such as when glucose, cholesterol, and blood pressure increase (secondary mediators). After living enough years with those processes uncontrolled, people can develop chronic health conditions such as heart attacks, diabetes, and cancer, which are tertiary disease outcomes. The composite score of allostatic load needs to include indicators of both primary and secondary biomarkers, because both are necessary pre-requisites to cause the final health outcomes (McEwen, 2003).

The allostatic load theory makes intuitive sense. Consider a simple example- maintaining your house. If the air conditioning fails, the whole house gets warm and humid. When things are hot and humid, the drywall and wood begin to rot, compromising the structural integrity of the home. Failing walls make it easy for rodents and termites to get into the house, where they chew holes through the roof and electrical wires. Eventually the whole house just collapses. One structure does not break in isolation- the whole system is affected. This analogy illustrates the allostatic load paradigm and how stress breaks down all the interdependent systems of the body. The stress response sets a few biomarkers out of their normal bounds, other parts of the try to compensate, and it continues down the chain.

Contribution/ Gap in the Literature

In sum, I believe this dissertation will make a valuable contribution because it bridges two distinct fields and gives the medical community a biologically plausible model to explain a

phenomenon that social scientists have been documenting separately for decades: the link between stigma/ disadvantaged social status and poor health outcomes, which is a necessary step to move the field forward. Crimmins and Seeman (2004) call for the need for comprehensive studies that consider both psychological and biological perspectives. They conceive of this body of work as a mediating pathway from demographic and psychosocial factors to biological risk markers to health outcomes. The authors argue that future research should prioritize more advanced modeling tools that can account for psychosocial, biological, and behavioral variables, as well as test mediation pathways, work that includes biomarkers representing multiple different bodily systems, and work on genetic factors.

Gehlert et al. (2008) have argued that future research should consider what they termed the "complete downward causal chain" to fully understand health disparities. They state that a complete view should start with the most upstream determinants (discrimination), consider how that drives hypervigilance, isolation, depression, etc., track how that triggers stress hormones, and then trace the impact that has on cell survival and other outcomes of interest downstream. They use the example of disparities in breast cancer mortality for African American women to illustrate how the complete knowledge loop could be applied by researchers (Gehlert et al., 2008).

Similarly, Miller, Chen, and Cole (2009) have published a complete manifesto of what is needed to advance our understanding of psychosocial determinants of physical health. They argue that in order to fully close this knowledge gap, researchers need to build up a body of evidence covering four key areas: 1) The association between the psychosocial stressor and disease, 2) a relationship between the psychosocial stressor and physical intermediaries (that is, biomarkers), 3) a description of the biological chain of causality (this hormone signals that cell,

which invokes that response, and destroys this thing, and so on, up to the point of disease), and finally 4) research that combines all of those three. The authors state that, traditionally, studies have looked at single risk factors (e.g., obesity) or single biomarkers (e.g., cortisol) in isolation, but comprehensive studies that examine the complete picture are direly needed to fully understand the impact of stress on the body. They further advocate that researchers need to go one step further to assess the "intrapsychic response" that individuals have to distal stressors (e.g., low SES) because that response is an important determinant of whether, or to what degree, the biologic intermediaries are activated. Note that this argument mirrors what social psychologists Lazarus and Folkman (1987) said about cognitive appraisal of stress. The group reports that the tools they expect will most help with innovation in this area are advanced statistical modeling to test mediation pathways, noninvasive imaging and biomarker capture, genome mapping, and lastly meta-analyses (Miller et al., 2009). Note that these largely overlap the priorities put forth by Crimmins and Seeman (2004).

Aside from advancing specific scientific knowledge on this topic, another benefit of bridging these two fields is that it may help sexual minority researchers gain credibility with the larger public health powerhouses that control access to data and funding, something they have continued to struggle with. For example, Sell and Holliday (2014) have discussed how, initially, the only way researchers got questions about sexual orientation written into large national surveillance programs was by arguing it was necessary to control the spread of HIV, not because sexual minority health itself was intrinsically important. They further explain that administrators who conducted those surveys were afraid to include questions about sexual orientation after watching the National Health and Social Life Survey lose its funding for doing so (Sell & Holliday, 2014). In an update a few years after his initial criticisms, Sell (2017) further lamented

how the CDC, Department of Health and Human Services, and NIH have failed to enact policies requiring all surveys managed by them to ask about sexual orientation, like was done with race and requiring women to be included as human subjects. Patterson, Jabson, and Bowen (2017) confirmed how lack of such a requirement has led to a lack of data sources. In a systematic review, only 21 datasets were found to have asked about sexual orientation at the national level, with 43 found in total, including smaller local datasets. Other problems they identified were that more than 1/3 of those studies were conducted with youth under the age of 18, so there is less data available on adults across the lifespan. Another issue is that none of the studies intentionally over-sampled sexual minority participants, so their numbers may be under-represented (Patterson et al., 2017). Indeed, Roberston, Tran, Lewark, and Epstein (2017) estimate that studies that do not allow for anonymous self-administered survey methodologies are under-estimating the prevalence of sexual minority individuals by anywhere from 50 - 414%.

Voyles and Sell (2015) documented how not only is there a sampling issue, but there is also a funding gap. Projects on non-HIV related sexual minority health topics represented less than 1/20th of a percent of the NIH's funding portfolio in 2012. Perhaps even more shocking, the Institute on Minority Health and Health Disparities, one whose mission would presumably be sympathetic to the issue of sexual minority health disparities, funded just one single project on sexual minorities. Further, there were only 10 R01grants awarded the whole year for the topic (Voyles & Sell, 2015). Coulter, Kenst, Bowen, and Scout (2014) found a similar pattern looking across a 22-year period from 1989 to 2011, rather than just one fiscal year. About one-tenth of a percent of studies were on non-HIV topics, and 89% of those included only gay men.

The literature reflects what the major funding agencies have prioritized. In a review, Boehmer (2002) identified 3,777 articles published with sexual minority participants. Of those,

56% focused on HIV/ sexually transmitted diseases. Only 15 articles were on the topic of non-infectious diseases. Combining these two theoretical frameworks from the two fields may be what's needed to move the needle on this problem. Social psychologists may become more competitive for grant proposals by being able to include a biologically plausible mechanism for the health disparities they wish to study, while biologists may benefit from being able to better articulate what the impact of expensive biomarker studies is on human quality of life, outside of research on HIV. Both arguments are key components of a standard NIH grant proposal.

I believe that my dissertation fills the gap illuminated by several experts in the field, and accomplishes many of the key objectives they suggest to advance this area of science forward. Drawing on Miller et al.'s (2009) four-point list:

1) I have already reviewed in an earlier section all of the associations that have been found linking stigmatized sexual minority status to disparate health outcomes.

2) I will aim to test differences in biomarkers of allostatic load by sexual orientation.

3) In my literature review that follows, I will discuss what is known about the biological chain of causality for the core systems that comprise allostatic load, including the HPA axis, cardiovascular system, and immune functioning.

4) Using a structural equation modeling approach, I will combine all of these ideas by testing a series of mediation hypotheses that prospectively link sexual minority stress to biomarkers to health outcomes.

The theoretical frameworks I have chosen are appropriate because Meyer's (1995; 2003) model of chronic sexual minority stress accounts for both distal stressors (discrimination and victimization events), and the downstream "intra-psychic responses" to them (internalized stigma, identity concealment, rejection anticipation, perceived microaggressions). The allostatic

load model is ideal because it uses a composite of many biomarkers to account for the synergistic and counter-compensatory effects of stress on multiple bodily systems; it is also a cumulative measure, thereby documenting a dose-response relationship of increased exposure to sexual minority stress over time. I will take the largely converging recommendations about what is necessary to move science forward in the broad area of psychosocial stress and biomedical health, apply them specifically to the study of sexual minority stress, and then actually implement / test the ideas with my hypotheses.

In the sections that follow, I will first review what is known about the HPA axis and stress, because that is where the stress response begins. I will then review what is known about two important secondary bodily systems in the allostatic load model: the cardiovascular and immune systems. Finally, I will tie all three together to discuss what empirical work currently exists on allostatic load as a complete concept. For each system, I take a funnel approach: starting broad to explain the biological mechanistic causal pathways of the effect of stress on that system, reviewing evidence on the link between psychosocial stress in general and poor health outcomes, evidence on the link between marginalization/ discrimination of any kind and poor health outcomes, and finally drilling down to my specific hypothesis: the link between sexual minority stress and poor health outcomes. I took this broad funnel approach because there is relatively scant data on sexual minorities and biomarkers, and even fewer comprehensive sources that assessed enough biomarkers to get a complete composite of allostatic load. After thoroughly reviewing the literature, I will outline my specific hypotheses.

HPA Axis and SAM System

The HPA axis is where the stress response begins, and is thus the catalyst for allostatic load (Ron de Kloet, Joels, & Holsboer, 2005). The process begins when the amygdala, the part of

the brain that processes emotion and fear, registers that a person is stressed. The amygdala then activates the hypothalamo-pituitary-adrenocortical (HPA) axis, which is the part of the endocrine system that manages stress and begins what is commonly known as the fight/ flight response. The hypothalamus responds by secreting the neuropeptides vasopressin (AVP) and corticotropin-releasing hormone (CRH), which together activate the pituitary gland. The pituitary gland then secretes adrenocorticotropic hormone (ACTH). The blood carries ACTH down from the brain to the adrenal cortex, which is adjacent to the kidneys. ACTH stimulates the adrenal cortex to produce corticosteroids and catecholamines into the bloodstream. These are the classic stress chemicals: cortisol (corticosteroid), epinephrine (catecholamine), and norepinephrine (catecholamine) (Ron de Kloet et al., 2005), and represent the neuroendocrine component of the allostatic load model. These hormones make up three of the key allostatic load biomarkers. In short bursts, catecholamines do things that help the fight/flight response, such as increase the amount of glucose in the blood so that we have energy. Most metabolic processes are suspended to further free up energy for the fight, including temporarily suppressing the immune system and slowing down the cell life cycle. Consequently, new cells do not get created (proliferation) as quickly, nor do old cells get voided as they should (apoptosis). Naturally, too much of any of these responses over the long-term is bad for the body (Ron de Kloet et al., 2005).

In addition to the direct problems caused by too much corticosteroids, there is another, indirect, problem. The HPA axis has a negative feedback system built in, a way to turn off the stress response (Herman, Ostrander, Mueller, & Figueiredo, 2005). The corticosteroids that are flowing in the blood bind to specialized glucocorticoid and mineralocorticoid receptors, which are particularly abundant in the limbic system. The bound molecules can then affect a person's genes, changing how they are transcribed and expressed. Usually, the receptors just interfere with

the process of making ACTH, and without ACTH the whole stress response stops. Under normal circumstances, this is a good thing. However, with chronic stress, the body senses there are too many corticosteroids flowing and reduces the number of GR and MR receptors they can bind with, leading to the failed negative feedback loop described earlier.

Long term, corticosteroids can alter the transcription of other genes, and even change the structure of the brain, which can result in decreased volume of the hippocampus and prefrontal cortex, and increased volume of the amygdala (Vyas, Mitra, Roa, & Chattarii, 2002). Rats given corticosterone showed hypertrophy of the amygdala and increased anxiety, but no differences in their conditioned fear responses to a foot shock (Mitra & Sapolsky, 2008). Corticosteroids can also break down long term potentiation, the ability for synapses to communicate with each other, which impairs the ability to consolidate memories. Interfering with gene transcription can also negatively alter the reward system of the brain. Chronic stress has been shown to make dopamine feel less rewarding to the brain, and to prompt the brain to produce less of it, thereby compounding the risk for depression. Ultimately, the organs become overwhelmed, unable to counteract the effects of sustained excess corticosteroids (Herman et al., 2005).

Biochemistry explains the mechanism of how an overly stressed HPA axis damages the body at the cellular level. What can human studies tell us about how an overtaxed HPA axis manifests in relation to psychosocial stress? For individuals with chronic stress in the form of anxiety symptoms, the HPA axis habituates to the stress and we observe blunted stress hormones. In other words, the body becomes “numb” to the stress and just stops reacting to it. Steudte et al. (2013) found that PTSD patients had lower hair cortisol levels than healthy controls, and that the PTSD patients with the greatest number of traumatic events had lower cortisol levels than patients with fewer traumas. Hair cortisol (as opposed to saliva) is a particularly good indicator

of chronic stress because it reflects levels over the past three months (Russell, Koren, Rieder, & Van Uum, 2012). Similarly, Petrowski, Herold, Joraschky, Wittchen, and Kirschbaum (2010) found that after undergoing the Trier Social Stress Test (which involves giving a speech), healthy individuals showed a sudden temporary spike in cortisol levels, while individuals diagnosed with panic disorder showed flat cortisol slopes over the observation period. These are examples of people habituating to stress.

In contrast, some people are predisposed to over-react to novel stressors. For example, individuals with depression tend to display elevated levels of neuroendocrine markers. Heuser, Yassouridis, and Holsboer (1994) detected that depressed individuals have higher levels of CRH and ACTH compared to healthy controls. Purba, Hoogendijk, Hoofman, and Swaab (1996) looked at brain tissue of deceased patients who had major depression, and found that they had more vasopressin and oxytocin neurons than controls.

Irregular hormone levels do not affect just the clinical population, but anyone experiencing ongoing stress. Dettenborn, Tietze, Bruckner, and Kirschbaum (2010) observed that individuals who had been unemployed for a year or more had higher hair cortisol levels than employed participants. Karlen, Ludvigsson, Frostell, Theodorsson, and Faresjo (2011) tested healthy university students, and found that those who reported having a serious stressful life event in the past three months had significantly higher hair cortisol levels than those did not. They also found that the students' perceived stress ratings did not correlate with their cortisol levels. As an aside, the lack of relationship between self-rated stress and cortisol is fairly consistent. In a review, Hjortskov, Garde, Orbaek, and Hansen (2004) found no such relationship in eight out of 14 studies. It seems people are poor judges of how stressed they actually are. Not only can young people be affected physically by stress, but the consequences can be long lasting.

In an extensive review, Luecken and Lemery (2004) reported that children who had difficult upbringings due to high-conflict divorce, abuse, death of a parent, etc. exhibited elevated neuroendocrine functioning as adults.

Being a marginalized member of society is another form of psychosocial stress that can dysregulate the HPA axis. Evans and English (2002) compared school age children living in poverty to higher SES children and found that they had significantly higher levels of cortisol, epinephrine, and blood pressure. Busse, Yim, and Campos (2017) found that Latino ethnicity did not directly predict steeper cortisol reactivity, but it did indirectly when mediated by increased experiences of discrimination. Lantz, House, Mero, and Williams (2005) conducted a longitudinal study from 1986 to 1994 and found that being a racial minority, having an income less than $10,000 per year, and having less than a high school education each significantly increased the risk of mortality. Their longitudinal study did not include any biomarkers, however it is logical to surmise that neuroendocrine dysregulation is a mediating link to mortality.

Neuroendocrine Biomarkers in Sexual Minorities

Because the minority stress model encompasses processes that both reflect anxiety and depressive-like symptoms, it is plausible that we could expect to see either a blunted or hyper-sensitive neuroendocrine response in sexual minority individuals. Hatzenbuehler and McLaughlin (2014) used a unique multi-method approach to ascertain sexual minority stress, and then tested whether it predicted cortisol levels. They operationalized structural stigma by looking at state-level factors of where young adult participants grew up, such as how many same-sex households the state has, or how many anti-LGBT laws were in existence. They also assessed perceived stigma with a questionnaire. The participants then completed a modified version of the Trier Social Stress Test, where the topic of the speech was to “discuss an experience in which

you were rejected based on your sexual orientation" instead of being about a job. Following the task, cortisol was measured via saliva. The researchers found that participants who grew up in highly stigmatizing states exhibited significantly lower cortisol reactivity to the stress test than those in less stigmatizing states. Such a blunted cortisol response is consistent with the patterns exhibited by people with post-traumatic stress disorder. On the other hand, perceived stigma was not significantly correlated with cortisol (Hatzenbuehler & McLaughlin, 2014). This study is valuable because it is one of the only existing studies that directly measures sexual minority stress (as opposed to just sexual orientation) and a biomarker.

In a similar Canadian study, Parra, Benibgui, Helm, and Hastings (2016) assessed how self-reported gay-related stress and internalized homophobia predict cortisol reactivity, and how those variables in turn predict depression. They measured diurnal cortisol slopes, meaning they took measurements six times over the course of a day, instead of just once. Consistent with the results of Hatzenbuehler and McLaughlin (2014), they too found that participants with more gay-related stress had flatter cortisol slopes. In addition to this finding, cortisol also acted as a significant mediator between stress and depression. However, internalized homophobia, one of the proximal dimensions of the Meyer (2003) model, was not a significant predictor of cortisol.

DuBois, Powers, Everett, and Juster (2017) conducted possibly the only study of stress biomarkers among transgender men. They asked men who had recently begun the transition process and were taking testosterone to answer questions about transition related stress, coming out stress, and public bathroom stress, as well as just general stress. All three of the gender stressors were positively correlated with higher cortisol levels upon wakening, but transition stress and bathroom stress predicted steeper falling cortisol slopes, instead of the blunted response pattern that others have found. DuBois et al. (2017) attribute the unexpected decreasing

cortisol slopes to a sign of resilience in the transgender men. Yes, they are being exposed to stress, as evidenced by the high morning cortisol, but the participants are coping with that stress so their bodies are able to adjust it to normal by bedtime.

Another possibility to consider though is the role of the testosterone therapy itself. The researchers did include length of time on testosterone as a control variable in their analyses. The authors' justification for doing so is that the longer one is on testosterone, the more their outward appearance matches their sense of true self, and the more they are able to "pass" in public, thus it is a variable indirectly representing minority stress (DuBois et al., 2017). Something they do not take into account though is that testosterone is known to downregulate the HPA axis (Oyola & Handa, 2017). Without a control group of transgender-identified individuals who have not had any exposure to testosterone therapy it is difficult to determine what role testosterone is playing. Further research would be needed to verify what is actually driving the steeper cortisol slopes that DuBois et al. (2017) observed.

One novel study explored how the constructs of biological sex and gender are indubitably intertwined with sexual orientation, and how they each might impact cortisol in ways that are additive to the sole effects of orientation. To assess gender, Juster et al. (2015) asked participants how much they identify themselves with traditionally masculine/ feminine traits. For sex, they measured levels of sex hormones. They then categorized people as being disclosed (i.e. having shared their sexual orientation with others) or non-disclosed. The researchers then gave a modified Trier Social Stress Test (TSST), controlled for the influences of the above as covariates, and measured cortisol responses. They found that all women started out the day with similar cortisol levels, but after the TSST, the sexual minority women had much higher levels than did the heterosexual women. For men, the sexual minority group had overall lower absolute levels,

but they also had a very flat slope, seemingly unaffected by the TSST. The heterosexual men showed a more typical peak shortly after the task, followed by a steady decline back down to their original starting values (Juster et al., 2015). Biomedical researchers have long understood that physical sex differences often lead men and women's bodies to respond differently, but we are only just beginning to understand the nuances of how the social manifestations of gender and sexual orientation are interwoven with the physical drivers of sex differences.

It is important to point out a significant limitation with the current literature on the neuroendocrine functioning of sexual minority individuals, which is that all of the studies described measured cortisol only. Typically, multiple indicators of the neuroendocrine system should be used, such as norepinephrine, epinephrine, and DHEA-S, in addition to cortisol (Juster et al., 2010). A full summary of all sexual minority biomarker studies discussed in this literature review is provided in Table 1. Having just discussed the HPA axis, I will now move on to the secondary components of the allostatic load model, the cardiovascular and immune systems.

Cardiovascular System

Cardiovascular disease is an umbrella term that encompasses a number of different conditions affecting the heart and its surrounding blood vessels. These conditions can include myocardial infarction (heart attack), stroke, hypertension (high blood pressure), arrhythmia (irregular heart beat), coronary artery disease, or congestive heart failure (heart does not pump adequately) (AHA, 2017). The underlying source of most of those conditions is atherosclerosis- when the arteries harden and get blocked by fatty build ups of plaque (Lagraauw, Kuiper, & Bot, 2015). Atherosclerosis is problematic not only for the obvious reason that the body must work much harder to force blood to squeeze through smaller and smaller arteries. It is also problematic because if the plaque ever breaks off and begins to circulate, it could become a clot that fully

blocks blood vessels, triggering the big events of heart attack or stroke. Therefore, understanding the causes and mechanisms of cardiovascular disease necessitates understanding the development of atherosclerosis (Lagraauw et al., 2015).

There are several different ways in which chronic stress contributes to the development of atherosclerosis. The first process occurs when a person is under stress and the kidney secretes renin, which then signals the renin-angiotensin-aldosterone system (RAAS) (Lagraauw et al., 2015). The RAAS is solely responsible for regulating blood pressure. Of course, when it is being activated all the time, blood pressure never really gets the opportunity to decline, resulting in a state of hypertension (Lagraauw et al., 2015).

Another way that chronic stress can lead to atherosclerosis is through endothelial dysfunction (Baeyens, Bandyopadhyay, Coon, Yun & Schwartz, 2018). Endothelial cells are the cells that line the inside of blood vessels. They are highly adaptive by nature, because different parts of the body and different kinds of blood vessels have different ideal blood flow levels they need to maintain. If blood flow is too far outside of the ideal range for what the endothelial cells need, they will activate inflammatory pathways in an attempt to get things under control (Baeyens et al., 2018). The activated immune cells have the side effect of causing more plaque to be created, while the caps of existing plaque deposits will weaken and struggle to stay in place. This weakening happens because the extra circulating immune cells (leukocytes in particular) can bind very easily with endothelial cells, forming an adhesion on the blood vessel that restricts blood flow (Baeyens et al., 2018).

Lastly, diabetes, a metabolic disorder, can also contribute to atherosclerosis (Chait & Bornefeldt, 2009). Metabolic biomarkers are also considered secondary mediators, like cardiovascular and immune markers, in the allostatic load model. Diabetes directly causes

problems in the body by producing too many molecules that consume all of the freely available nitric oxide, which is the chemical that prompts blood vessels to dilate and let more blood through. Vessels failing to dilate causes chronically slowed blood flow in diabetes patients. Indirectly, diabetes also causes problems because it acts as a separate additional activator of inflammation (Chait & Bornefeldt, 2009). Through all of these interacting pathways, chronic stress weakens arteries, slows blood flow, and increases clots, which after many years, culminates in clinically observable cardiovascular disease.

Although in the allostatic load framework the only biomarkers that are technically classified under the cardiovascular system are blood pressure, and pulse, many of the biomarkers from the other categories are known risk factors for cardiovascular disease because they contribute to atherosclerosis. Those would include other markers such as cortisol, glycosylated hemoglobin, BMI, cholesterol, and DHEA-S (see Kyungeh et al., 2015 for a review of commonly used CVD biomarkers). Therefore, in practice, much of the research on cardiovascular disease does assess those other biomarkers. Cortisol (a neuroendocrine biomarker), for example, is a particularly strong predictor of cardiovascular disease; In a longitudinal study, Vogelzangs and colleagues (2010) found that people with the highest cortisol levels were five times more likely to have died from cardiovascular disease after only a six-year follow-up. This finding serves to highlight why comprehensive measures that include as many biomarkers from all of the bodily systems are necessary to get a complete understanding of physical health.

In addition to research on the pathological mechanisms of atherosclerosis, there is abundant epidemiological and animal-model evidence that support the association between chronic psychosocial stress and cardiovascular disease. Over a dozen different studies have

shown that inducing stress in mice by making their cage physically uncomfortable, introducing intruders, socially isolating them, and separating infants from the mother, consistently results in atherosclerotic lesions and increased plaque development (Lagraauw et al., 2015).

In humans, the Framingham Heart Study discovered as early as 1978 that having a Type A personality was associated with increased prevalence of heart disease, even when controlling for factors such as smoking, blood pressure, and age (Haynes, Feinleib, Levine, Scotch, & Kannel, 1978). Similarly, the INTERHEART study examined nearly 25,000 people across all continents except Antarctica (Rosengren et al., 2004). The people who already experienced a heart attack reported more work stress, home stress, financial stress, and major life events than did controls who had never had a heart attack. The heart attack patients also reported feeling more depression symptoms in the previous 2 weeks. Each of the stress factors had odds ratios between roughly 1.5 and 2.4, after controlling for other traditional risk factors (Rosengren et al., 2004)

A recent meta-analysis, conducted by Kivimaki and colleagues (2012), pooled data from several cohort studies and found that job stress is consistently associated with an increased risk for cardiovascular disease. In line with those findings, Gustad et al. (2014) reported that individuals with major depression are at nearly 4.5 times higher risk for heart failure than people who are not depressed. Even more alarming, stress in childhood has been found to carry through to adulthood. Dong et al. (2004) found that as the number of adverse childhood experiences (i.e., abuse and neglect) increases, so too does the risk for heart disease. Numerous studies across countries and decades have tied various sources of psychosocial stress to heart problems.

Beyond the enormous body of evidence documenting the link between general psychosocial stress and cardiovascular health, there are additional studies that document an

increased risk for disadvantaged groups. African Americans are more likely to die from cardiovascular disease than whites, and also carry a higher burden of risk factors such as diabetes (Leigh, Alvarez, & Rodriguez, 2016). Goodman, McEwen, Huang, and Adler (2005) found that even in adolescence, teens whose parents had low education already showed worse biomarker profiles (higher insulin, glucose, cholesterol, waist circumference, and BMI) than kids with more educated parents. Socioeconomic inequality in general has been shown to be predictive of disparities in cardiovascular disease (Brunner, 2017). These differential risk patterns for marginalized groups provide support for a minority stress contribution to cardiovascular disease.

Cardiovascular Biomarkers in Sexual Minorities

Everything we know about differences in cardiovascular biomarkers by sexual orientation comes from two sources. One is the National Longitudinal Study of Adolescent Health (Add Health). Data collection began in 1994 with students who were in 7^{th} – 12^{th} grade at the time (Harris et al., 2009). The study includes survey data at all time points, and biomarker data for Wave IV. Wave IV was conducted in 2008- 2009. Wave V was still ongoing data collection during 2018, so Wave IV is the most recent data available to researchers. The complication with using Add Health data to study cardiovascular disease is that participants were only aged 20-32 in the latest Wave IV (Harris et al., 2009).

The second source of data on this topic is the National Health and Nutrition Examination Study (NHANES). The NHANES is a cross-sectional study, for which a new sample is drawn every year (CDC, 2019). It began in 1999 and continues today. The study involves both self-report surveys and physical health exams that are conducted in mobile clinic centers. Both children and adults are open to participation, but the studies discussed here involving biomarkers only include data from adults aged 20-69.

Findings on how cardiovascular risk varies due to sexual orientation is inconsistent- some articles report significant differences by sexual orientation while others do not. One study, using Add Health data, looked at a composite score of multiple biomarkers of cardiovascular risk (blood pressure, waist circumference glycosylated hemoglobin, C-reactive protein, and pulse) and found that heterosexuals did not differ significantly from the LGB group (Hatzenbuehler, Slopen, & McLaughlin, 2014). Despite an insignificant main effect, the researchers did find that sexual orientation significantly interacted with the number of cumulative stressful life events an individual experienced. For both gay/ bisexual men and lesbian/ bisexual women, those with the highest numbers of stressful life events had significantly higher cardiometabolic risk (Hatzenbuehler et al., 2014). The inverse of this finding was not true; heterosexuals with high stress were not at any greater risk for cardiovascular disease. This lends support to Meyer's (2003) sexual minority stress theory, which says that stress from one's marginalized identity is additive above and beyond regular life stress.

While that team did not find significant differences for the composite biomarker score, in a separate article they published using the same dataset, they did find differences when looking at each of the biomarkers individually (Hatzenbuehler, McLaughlin, & Slopen, 2013). Gay/ bisexual men had higher diastolic blood pressure, pulse, and C-reactive protein than heterosexual men. They had lower glycosylated hemoglobin than the heterosexual men. Unexpectedly, lesbian/ bisexual women actually had lower levels of C-reactive protein than heterosexual women. None of the other comparisons were significant (Hatzenbuehler, McLaughlin, & Slopen, 2013).

In another study using the Add Health dataset, a different group of researchers calculated a composite score of relevant biomarkers (Clark et al., 2015). The composite is designed to

reflect the 30-year risk for cardiovascular disease, and the method for it was developed as part of the Framingham Heart Study (Pencina, D'Agostino Sr., Larson, Massaro, & Vasan, 2009). The measures they included in the composite were systolic blood pressure, BMI, usage of hypertensive medications, smoker status, and diabetes status. This approach deviates somewhat from that of an allostatic load hypothesis, which recommends using actual biomarker measurements instead of a binary diagnosis status because the goal is to detect anomalies even before they reach clinical significance (e.g., use hemoglobin instead of yes/no for diabetes diagnosis). Using the Framingham protocol, the researchers found that women who self-identified as mostly homosexual had higher 30-year risk scores than did the heterosexual women (Clark et al., 2015). They did not find any significant differences between homosexual and heterosexual men. In addition to differences in how they modeled the biomarkers, this study also differs from the others referenced that used this same dataset because they separated out sexual orientation by the categories offered to self-select on the survey: heterosexual, mostly heterosexual, bisexual, mostly homosexual, and homosexual, whereas others pooled together all of the sexual minority men and women, respectively.

In a fourth study still using the same Add health dataset, Harper (2016) looked at the Framingham 10-year risk for cardiovascular disease (as opposed to the 30-year risk score described above.) Harper (2016) included systolic blood pressure, BMI, smoking status, and diabetes status to calculate the composite. In addition to the 10-year risk score, the Framingham method also provides an algorithm to calculate vascular age in relation to actual age, which was the secondary dependent variable. This study pooled all of the sexual minority individuals together, and did not separate them by gender. Sexual orientation was not found to be a significant predictor of 10-year cardiovascular disease risk or of vascular age (Harper, 2016).

The inconsistent findings reported here, from Add Health datasets, about whether sexual orientation is a significant predictor or not could be simply due to the fact that any changes in cardiovascular health are too small to detect so early in life, because the Add Health participants were only aged 20-32. Crimmins and Seeman (2004) have found from their own work (on allostatic load collectively, not just cardiovascular biomarkers) that differences between at-risk groups don't even become first detectable until between the ages of 20-30. They report that after initial onset, the slopes sharply steepen, making the differences between groups most pronounced between the ages of 35-65. After that, differences decrease, presumably because individuals with the highest allostatic load scores die, creating survivorship bias (Crimmins & Seeman, 2014).

The next set of studies used NHANES data. Taking a similar methodological approach to Harper (2016), Farmer, Jabson, Bucholz, and Bowen (2013) analyzed the Framingham algorithm for vascular age as the main dependent variable of interest. It was calculated slightly differently though: variables used were HDL cholesterol, total cholesterol, systolic blood pressure, diabetes status, smoking status, and use of hypertensive medications. Only women were considered, and all of the sexual minority women were pooled together rather than separating out bisexuals vs. lesbians. Farmer et al. (2013) found that the sexual minority women had a significantly higher vascular age than did heterosexual women. Both groups' vascular age was greater than their actual age, but for the sexual minority women, the gap was significantly wider. Their vascular age was nearly 14% greater than their actual age (Farmer et al., 2013). In another study using men there was no significant difference in vascular age (Farmer, Bucholz, Flick, Burroughs, & Bowen, 2014). Bisexual men were found to have a higher Framingham risk score than heterosexual men, but no difference was found comparing homosexual men to heterosexual men (Farmer et al., 2014).

Caceres et al. (2018) also published an independent study of men using the NHANES 2001-2012 data. They looked at the same biomarkers that Farmer et al. (2013) did, but they examined them individually rather than as a composite. To assess cardiovascular disease, they utilized participants' self-reports of whether they have ever had any such conditions. The team found that there were no significant differences by sexual orientation for self-reported cardiovascular disease. Likewise, there were no differences between homosexual and heterosexual men on the biomarkers, but the bisexual men did differ. The bisexual men had higher rates of obesity, blood pressure, and glycosylated hemoglobin compared to heterosexual men (Caceres et al., 2018).

The lack of differences found for self-reports is consistent with what a recent systematic review reported. Caceres et al. (2017) noted that only four out of 23 self-report studies found significant differences by sexual orientation on the prevalence of cardiovascular disease. The remaining studies found no difference. Having just discussed the role of stress on cardiovascular biomarkers, as well as the inflammatory and metabolic issues that further feed into cardiovascular disease, I will now discuss in detail the immune system.

Immune System

Inflammation is the body's defense system for pathogens, physical trauma, as well as stress. There are two pathways for which stress can trigger the immune response (Glaser & Kiecolt-Glaser, 2005). Stress activates the HPA axis and the sympathetic nervous system to set in motion the fight or flight response. During this process, the amygdala releases neuropeptide substance P (Black, 2002). While substance P is not typically discussed in regard to the HPA axis, it triggers the immune system's own version of the fight/flight response, the acute phase response. It is the immediate initial reaction to a threat, believed to be designed to help animals

fight infection, such as after battling for a mate. Substance P stimulates the immune cells to produce cytokines, and it triggers degranulation of mast cells into inflammatory mediators (e.g., histamine). This process is coined the chemical binding pathway for inflammation (Black, 2002). Substance P can also propagate the stress response by increasing levels of the stress hormones (CRF, ACTH, AVP) that signal the HPA axis.

Therefore, communication is a two-way street between the HPA axis and the immune system. Corticosteroids produced by the HPA axis can, in turn, worsen inflammation by telling immune cells to travel to other parts of the body, where they promote vascular adhesion (where monocytes bunch up and stick to/ clog the inside of blood vessels), and resist the effects of insulin (thus also worsening metabolic dysfunction). The immune system also suffers from the same problem that the HPA axis does under chronic stress, which is that the negative feedback system designed to shut everything off fails (Black, 2002).

Scientists are also coming to understand that the sympathetic nervous system itself can physically trigger the immune response via neuronal signaling. Glaser and Kiecolt-Glaser (2005) refer to this as the "hard-wiring" mechanism. Black (2002) explains how animal studies have experimentally demonstrated support for this. Such studies show that severing sympathetic nerves (post-ganglionic sympathetic neurons in particular) will completely stop inflammation from spreading from one joint to the other, and that it will eliminate nerve pain in the affected area. It has also been observed that inflammatory conditions are more likely to occur in areas of the body where those nerves are denser. Black (2002) further points out that, when considering the physical structure of post-ganglionic sympathetic neurons, it makes intuitive sense that they would be involved in inflammation. The endings of the neurons contain neuropeptide Y and corticotropin releasing factor (stress hormones), as well as interleukin-6 (cytokine). Researchers

have also discovered that electronically stimulating the C-fiber nerve (part of the sympathetic nervous system) causes the neuron to conduct signals opposite of the usual direction, which incites an inflammatory response, coined the sympathetic innervation pathway (Black, 2002).

Because there are so many different immune cells, cytokines, and mediators involved in the inflammation process, there are dozens of possible biomarkers one could examine. Indeed, Juster et al. (2010) document 12 biomarkers of inflammation in their systematic review of allostatic load. However, there are a small handful of biomarkers that researchers in this area focus on most commonly. The first two are proteins. C-reactive protein is created by the liver in direct response to IL-6 levels (Hansel, Hong, Camara, & von Kanel, 2009). In addition to being useful as an inflammation biomarker, C-reactive protein is also used in cardiovascular research because it has been associated with three times increased risk of heart attack (Black, 2002).

Another protein is fibrinogen. Fibrinogen is also produced by the liver to help repair damaged tissue. A side effect of fibrinogen is that it raises cholesterol levels, increasing the formation of plaque in arteries, and promoting blood clotting. For these reasons, fibrinogen has also been used as an indicator of cardiovascular health in addition to inflammation (Black, 2002). Once again, there is significant crossover between the effects of inflammation and cardiovascular health for all of the biomarkers (see Aiello & Kaplan, 2009 for a complete review of how the two systems interact). This crossover further highlights the need for a holistic vantage point- such as allostatic load, rather than looking at these systems as operating independently.

Three biomarkers of inflammation that are very frequently studied are cytokines. Cytokines are peptides whose function is to signal immune cells (Hansel et al., 2009). They can be pro-inflammatory or anti-inflammatory. Naturally, I will focus on the pro-inflammatory ones, as these are associated with chronic stress: interleukin-6, interferon, and tumor necrosis factor.

Of those, interleukin-6 has received the most attention, likely because high levels of it can be circulating well before someone is symptomatic (Hansel et al, 2009).

These five immunologic biomarkers have been associated with many different forms of psychosocial stress. Eraly et al. (2014) found that among marines deployed to war zones, their levels of C-reactive protein increased significantly after deployment. Toker et al. (2005) similarly found that women experiencing job burnout had higher levels of C-reactive protein and fibrinogen. Likewise, Kiecolt-Glaser et al. (2003) followed caregivers of loved ones with dementia and found that their interleukin-6 levels were quadruple those of the controls by the end. In another longitudinal study, Danese, Parlante, Caspi, and Talyor (2007) found that children who faced maltreatment had significantly higher C-reactive protein levels as adults.

In addition to general psychosocial stress, increased markers of inflammation have also been observed among various marginalized groups. Stepanikova, Brand Bateman, and Oates (2017) found that race, socioeconomic status, and perceived discrimination all impacted inflammation, finding that black individuals had significantly higher levels of interleukin-6 and fibrinogen than white individuals. Higher education was associated with lower levels of fibrinogen, while higher perceived discrimination was associated with higher levels of fibrinogen. The researchers also considered E-selectin and C-reactive protein levels as outcomes, but found no significant differences after controlling for covariates (Stepanikova et al., 2017). Conversely, Elliot and Chapman (2016) did find that people with lower socioeconomic status (a composite of education, income, and job prestige) had significantly higher levels of C-reactive protein, but no significant differences for interleukin-6. Where Stepanikova et al. (2017) did not find differences for E-selectin, Friedman, Williams, Singer, and Ryff (2009) did. They found significant main effects for both major discrimination (e.g., being denied a home loan or fired

from a job) and everyday discrimination (e.g., being followed at a store, receiving poor service at a restaurant), with higher levels predicting higher concentrations of E-selectin. They also found a significant interaction effect for discrimination and gender. The interaction revealed that the association is stronger at the highest discrimination levels for men, but for women, there is no difference.

Immune Biomarkers in Sexual Minorities

Research on inflammation biomarkers in sexual minority populations is relatively scarce. At the time of this writing, I was only able to identify three articles on the topic. In one study, Everett, Rosario, McLaughlin, and Bryn Austin (2014) used Add Health data (previously described) to examine differences in C-reactive protein and Epstein Barr virus. As a reminder, the Add Health study is focused on young people, with participants ranging in age from 20-32 at most recent observation. Everett and colleagues (2014) did not find a significant main effect for sexual orientation, however they did find the orientation by gender interaction to be significant. The interaction revealed that homosexual and bisexual men had higher levels of C-reactive protein than heterosexual men. Among women, they found that lesbian and bisexual women actually had lower levels of C-reactive protein than heterosexual women, and no differences for Epstein Barr virus (Everett et al., 2014).

The authors present a "gender non-conformity hypothesis" to explain the somewhat unexpected results for sexual minority women (Everett et al., 2014). Typically, ignoring sexual orientation, women consistently have higher C-reactive protein levels than men in the general population. In this study, that was not the case for sexual minority women. Essentially, the authors assert that lesbian women tend to adapt more traditionally masculine personality characteristics, and thus they may be gaining some protective factors from that. Or conversely,

that gay men who adapt more feminine traits tend to be victimized more for their gender-nonconformity, and thus that added stress could be causing the excessive inflammation (Everett et al., 2014). While specifically testing that hypothesis is beyond the scope of this dissertation, it is an intriguing supposition to keep in mind when evaluating somewhat variable results on the topic.

Doyle and Molix (2016) tested for differences in interleukin-6 and found results that are consistent with the gender non-conformity hypothesis, although they did not set out to explicitly test it. They found that lesbian women had lower levels of interleukin-6 than gay men (note their sample did not include a heterosexual comparison group). The team also tested if perceived discrimination and "covering" (the degree to which someone who is out tries to downplay their gay-ness) would also predict interleukin-6 levels. Among gay men, more discrimination was associated with higher interleukin-6, only when they did less covering. The distinction between covering and coming out is important when interpreting the results of this study. The minority stress model says that the less out people are (typically measured as how many people a person has come out to) should yield worse health outcomes. However, in this study, Doyle and Molix (2016) are arguing that all of the participants are already fully out, and so now "covering" has protective effects because participants are essentially being less flamboyant about their gay-ness. They are not violating gender norms and drawing excess attention to their gay-ness, which would make them more likely to be victimized.

The final study on this topic actually looked at markers of HIV progression (Norcini Pala, Hart, & Steca, 2017). It is appropriate to consider within the context of inflammation because one of the key clinical metrics for managing HIV+ patients is CD4 count- the number of white blood T-cells a person has. Additionally, the HIV virus is known to increase levels of cytokines

(e.g. interleukin-6) of interest. Furthermore, Norcini Pala et al. (2017) situate their study in the context of stress and how HIV progression can be worsened by continuous activation of the HPA axis. They found that among HIV+ men, experiencing more enacted stigma was associated with higher viral loads. Likewise, greater internalized homophobia predicted higher viral loads and lower CD4 counts (Norcini Pala et al., 2017).

Allostatic Load

As can be seen from the body of literature just described, the different bodily systems don't exist within independent silos. Metabolic dysfunction, such as having diabetes, can be a contributing cause of inflammation. Inflammation itself causes atherosclerosis, a powerful risk factor for cardiovascular disease. Anthropometric abnormality, that is, being overweight/ obese, of course contributes to all of those. Despite all of this interdependence, researchers often choose to specialize in/ and only consider one system in their work. This leaves our understanding of the link between stigma and health somewhat disjointed. Allostatic load theory brings clarity to that disjointedness by allowing us to study the systemic impact of social stress, with each of the separate bodily systems dynamically interacting. The remainder of my literature review will document what such comprehensive work currently exists.

The earliest comprehensive study of allostatic load- one that measures the functioning of all of the key bodily systems jointly- comes from the MacArthur Studies of Successful Aging (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). The MacArthur study is a longitudinal study of elderly adults. New participants are enrolled when they are between 70 and 79 years-old, and it is a community-based study rather than a clinical sample. As part of the study, numerous biomarkers are recorded.

Seeman et al. (1997) looked at the biomarker data available from the MacArthur study and tried to pare it down to what they thought were the 10 most important parameters. The parameters were selected to represent all of the major bodily systems described in the theoretical model of allostatic load - cardiovascular, anthropometric, neuroendocrine, metabolic, and immune markers. With these, they designed the composite allostatic load score. The rationale behind pushing for composite measures is that none of the parameters may have reached clinically significant thresholds on their own yet, but if they are all slightly out of range, a composite score would detect that (and hopefully predict poor outcomes sooner than otherwise would have been diagnosed). The score is created by binary coding each of the 10 biomarkers. If an individual is in the worst quartile of the sample, they are coded as a one for that parameter. Otherwise, they get a zero. These tallies are then summed up to create the allostatic load composite, which ranged from zero to ten because that is how many biomarkers they assessed (Seeman et al., 1997). Note that while they included ten to be a manageable number in that first study, the authors are proponents of using as many as feasible.

Since the initial operationalization of allostatic load, it has been validated dozens of times in many different populations. The model has been tested in countries such as Germany, Australia, Taiwan, Sweden, Finland, Norway, China, and Scotland (see Juster, McEwen, & Lupien, 2010 for a comprehensive review). In the beginning stages of research in this area, the primary utility of an allostatic load score was for predicting mortality (e.g. Seeman, McEwen, Rowe, Singer, 2001; Seeman, Crimmins, Huang, Singer, Bucur, Gruenewald, Berkman, & Reuben, 2004; Goldman, Turra, Glei, Seplaki, Lin, & Weinstein, 2006). Over the years, the research agenda has expanded to include many other health outcomes: Higher allostatic load has

been consistently linked with worse physical health status, declines in physical functioning, greater fatigue, and cognitive decline, among others (Juster et al., 2010).

Across time, different studies have not always been consistent about which biomarkers were included; some have included as few as four (Gersten, 2008), while others have included up to 17 biomarkers (Bellingrath, Weigl, & Kudioelka 2009). Likewise, some variations have been introduced about how to score the parameters. Some researchers have used a more restrictive threshold (the worst 10%) as the cutoff rather than quartiles. Other researchers have used a 2-tailed approach, where biomarkers that are on the extreme high or low end can be scored a one, while others have used summed z-scores to create the composite score. The original formula is still by and large the most common scoring technique though (Juster et al., 2010).

As our understanding of allostatic load has evolved, so too has our interest in connecting it to different kinds of psychosocial stress. Increases in allostatic load have been associated with many different kinds of life stress, including poor working conditions/ burnout (Danhof-Pont, van Veen, & Zitman, 2011; Schnorpfeil, Noll, Schulze, Ehlert, Frey, & Fischer, 2003; Juster, Sindi, Marin, Perna, Hashemi, Pruessner, & Lupin, 2011), caregiving for people with dementia (Clark, Bond, & Hecker, 2007; von Kanel, Dimsdale, Patterson, & Grant, 2003; Roepkie, Mausbach, Patterson, von Kanel, Ancoli-Israel, Harmell, Dimsdale, Aschbacher, Mills, Zielger, Allison, & Grant, 2010), being a parent of a child with a life-threatening illness (Glover 2006; Glover 2008), or having a history of adverse childhood experiences (Danese & McEwen, 2012). The link between chronic stress and allostatic load has been supported across many different populations/ cultures, and many different types of psychosocial stressors.

Extending that concept, a whole body of literature has developed in the last 10 years documenting the connection between social disadvantage/ stigma and allostatic load. There are

many studies documenting the connection between race, low SES, neighborhood disadvantages (inner cities, rural areas) and allostatic load. See Beckie (2012) for a complete review. As an example, Duru, Harawa, Kermah, and Norris (2012) used data from the NHANES and found that blacks had higher allostatic load scores than whites, and that allostatic load accounted for differences in mortality risks. Parente, Hale, and Palermo (2013) found that increased allostatic load is associated with a history of breast cancer in black women. In Sweden, a longitudinal study showed that living in disadvantaged neighborhoods is associated with long-term increases in allostatic load. Brody et al. (2013) found that among blacks in the rural south, low SES and high allostatic load are traits that form a "physical health vulnerability profile." Similarly, Hawkley, Lavelle, Berntson, and Cacioppo (2011) found that across all racial groups living in Chicago, lower SES was associated with increased allostatic load.

Allostatic Load in Sexual Minorities

Given the consistent pattern of different disadvantaged social statuses exhibiting increased allostatic load, it is logical to deduce that sexual minorities (lesbian, gay, bisexual, and transgender individuals) would also experience greater allostatic load relative to the majority group (heterosexual individuals). The allostatic model has not been as thoroughly tested in sexual minority populations compared to other groups. To my knowledge, there have only been seven empirical studies (published and unpublished) conducted examining the role of sexual orientation on allostatic load, and several come from the same datasets. One of the most commonly used data sources for these studies is the National Health and Nutrition Examination Survey (NHANES), previously described.

Adams (2008) examined the 2001-2004 NHANES data in an unpublished thesis. He calculated odds ratios of having an elevated allostatic load score and found that sexual minority

individuals were at a slightly increased risk compared to heterosexuals (OR = 1.299), but the difference was not statistically significant. When examining the biomarkers individually though, he found that sexual minorities had higher HDL cholesterol levels, and higher glycosylated hemoglobin (Adams, 2008). In another study of NHANES data (years 2005-2010), Arheart et al. (2013) reported similar results in a conference presentation. Sexual minority groups had higher mean allostatic load scores than did heterosexuals, however the differences were not statistically significant. In their analyses, the authors kept the lesbian, gay, bisexual, and other sexual orientation groups separate. It is possible they may have attained different results if they had pooled them together into one sexual minority group for greater statistical power. Mays, Juster, Williamson, Seeman, and Cochran (2018) looked at a full decade of NHANES data from 2001-2010, thus overlapping both Adams (2008) and Arheart et al. (2013). Mays et al. (2018) found that bisexual men had the highest allostatic load scores. Unexpectedly, they also found that gay men had significantly lower allostatic load scores than heterosexual men. There were no significant differences between bisexual, lesbian, or heterosexual women (Mays et al., 2018). The combined insights from these analyses of the NHANES suggest there could be some differences by sexual orientation that the smaller data pools were unable to detect.

In one of the few original research studies on this topic, Juster, Grant Smith, Ouellet, Sindi, and Lupien (2013) recruited their own sample of 257 lesbian, gay, bisexual, and heterosexual participants. It was a convenience sample of young and middle-aged adults from Montreal. For their analyses, they pooled gay and bisexual men together as one group, and did the same for women. They found the same surprising pattern as in the NHANES studies- that sexual minority men had significantly lower allostatic load scores than heterosexual men. Sexual minority women had mean allostatic load scores that were higher than heterosexual women, but

the gap was not statistically significant. Such non-significant differences also existed for nondisclosed participants, who had higher scores than disclosed participants (Juster et al., 2013). The trend is consistent with Meyer's (2003) minority stress theory, which says that identity concealment is a major source of stress for sexual minority individuals who are nondisclosed.

In a follow up to the above study, using the same sample, Juster et al. (2015) examined how perceived stress and coping mechanisms relate to allostatic load. They asked participants to think back to when they were first beginning to realize they were LGB and when they first started telling others about their identity- how did they cope during that time? The participants who reported using avoidant coping strategies during past identity formation felt significantly more perceived stress, reported experiencing more daily hassles, and had significantly higher allostatic load scores at the time of the study (Juster et al., 2015).

In an unpublished presentation, Krueger, Hatzenbuehler, and Upchurch (2015) reported on Add Health data (previously described.) They only included LGB individuals, so there is no comparison group. The variable of interest in this study was discordance- a state in which the participant's self-described sexual identity is incongruent with their reported sexual behaviors or romantic attractions. The results were mixed. Identity-attraction discordant men (men who see themselves as bisexual or homosexual but are romantically attracted to the opposite sex) had significantly higher allostatic load scores than concordant men. Identity-behavior discordant men (men who see themselves as bisexual or homosexual but who have had opposite sex sexual partners) though, had significantly lower allostatic load scores. Among women, being identity-attraction discordant was associated with lower allostatic load (Krueger et al., 2015). It seems counterintuitive that the researchers chose to exclude people who described their identity as heterosexual. Given a whole body of literature that discusses the struggles of "being on the down

low" (a term typically used in black communities to describe men who identify as straight but also sleep with men secretly), I would expect the highest risk group to be individuals who describe their identity as heterosexual but report same sex romantic attraction/ sexual encounters.

Finally, in a very unique study, Glover, Williams, and Kisler (2013) assessed allostatic load in an especially vulnerable population: 117 HIV+ black men who reported having both male and female sexual partners in the past 90 days. In that group, HIV progression (measured both in years since diagnosis and via urinary neopterin levels) did not predict allostatic load. Post-traumatic stress disorder symptom severity did predict increased allostatic load though (Glover et al., 2013). It is remarkable that psychological stress was a greater driver of allostatic load than HIV, a virus that is known to independently cause premature aging and general "wear and tear" on the body.

The theme that emerges from this small set of studies is that using sexual orientation as the sole predictor of allostatic load tends to yield small effects. Including more nuanced predictor variables though, such as disclosure, perceived stress, and identity congruence is more likely to reveal differences in allostatic load. Sexual orientation is only a proxy for the true variable most researchers are trying to get at in this line of work- minority stress. Heterosexuals presumably have zero sexual minority stress, but in using a proxy we lose all of the variability in how much stress LGB individuals are actually feeling. Using measurement tools that allow us to begin to parse out variations in minority stress (even if imperfect), will better allow us to model a dose-response relationship of the effects on allostatic load. Knowing this, I will now propose a set of hypotheses that do aim to use better approximations of minority stress, and that utilize mediation models called for in the literature. An illustration of these hypotheses is presented in Figure 2.

Hypotheses

H1: I predict that sexual minority individuals will have higher allostatic load scores at time 2 and higher rates of cardiovascular disease, cancer, and chronic conditions at time 3 compared to heterosexual individuals.

H2: I predict that sexual minority individuals will experience more everyday discrimination than heterosexual individuals, and in turn, that people with higher everyday discrimination scores will have higher allostatic load scores, and that in turn, higher allostatic load will predict increased rates of cardiovascular disease, cancer, and chronic conditions. This is a sequential mediation pathway that has two intervening variables: X (sexual orientation) >> M1 (everyday discrimination) >> M2 (allostatic load) >> Y (cardiovascular disease, cancer, and chronic conditions).

METHOD

Overview of the MIDUS

Data for this dissertation come from the Midlife Development in the United States (MIDUS) study (Brim et al., 2019). The original intent of the project was to track "age-related variations in health and well-being" from a multi-disciplinary perspective. The project is a joint venture between the MacArthur foundation and the University of Wisconsin. It is a longitudinal study that began in 1995 and is still actively funded and continuing to collect data today. Three waves of data are currently available: Time 1 (collected from 1995-1996), Time 2 with biomarkers (collected from 2004-2009), and Time 3 (collected from 2013-2015).

Participants

The core sample of participants was recruited using a random digit dialing method in order to attain a nationally-representative sample (Brim et al., 2019). Participants were required to be between the ages of 25 and 74 at baseline in order to be eligible for the study. The other inclusion criteria were that participants must be English-speaking, live in the 48 contiguous United States, and not be institutionalized. After generating an initial random sample, the researchers then did some oversampling in major cities to ensure all groups were adequately represented. They also contacted siblings, especially twins, of the core sample to participate as well, which was done so that researchers interested in studying genetic effects would have comparison data. Everyone who participated in the prior wave was eligible to participate in the following wave. The MIDUS team reports that the study has an overall response rate of 81% (Brim et al., 2019).

For the purposes of this dissertation, selected participants were required to have completed the optional biomarker study in Time 2, and the survey in Time 3 to be included in analyses. This requirement is because testing a mediation pathway would be impossible without observation of the x, m, and y variables. A total of (n = 945) participants completed all three of those waves. Among those, 45 participants identified as a sexual minority and 899 identified as heterosexual. The sample is slightly more female (56%) than male (44%). White individuals comprised 91% of the sample. The average age of participants at time 1 was 45 years old. About half of participants had at least some college education. Significantly more of the participants reported being cigarette smokers (44%) than not (28%), and a lot of individuals skipped that question (28%). A summary of the demographic variables is presented in Table 2.

Measures

Sexual Orientation. Orientation was determined by how participants self-identify. Only three choices were offered, with no other option available. The full question reads "How would you describe your sexual orientation? Would you say you are heterosexual (sexually attracted only to the opposite sex), homosexual (sexually attracted only to your own sex), or bisexual (sexually attracted to both men and women)?" Individuals who identified as a sexual minority at any time point were counted in this group. For the present analyses, homosexual and bisexual individuals were combined into one sexual minority group in order to increase statistical power.

Everyday Discrimination (α = .97). The Everyday Discrimination Scale is a nine-item scale that asks about more day to day forms of discrimination (Williams, Yu, Jackson, & Anderson, 1997). This scale was selected as the best available indicator for sexual minority stress in the MIDUS survey. Some of the items are subtle, "You are treated with less courtesy than other people" while others are more severe, "You are threatened or harassed." The response

options ranged from 1 "*often*" to 4 "*never*." The scale was scored by reversing all of the items such that higher scores would indicate more discrimination, and then summing all of the items for each participant. Therefore, the span of scores ranged from 9 (lowest amounts of discrimination) to 36 (highest amounts of discrimination). Everyday discrimination scores at time 1 (the data collection period taking place during 1995-1996) were used in the present analyses.

Allostatic Load. For the purposes of this dissertation, allostatic load was operationalized as a composite of 15 biomarkers, assessed at time 2 (after everyday discrimination, but before the health outcomes). Biomarkers were selected on the basis of which ones appeared most frequently in the literature review from each of the five major bodily systems. I used the original scoring technique recommended by Seeman et al. (1997). The scoring technique involves calculating quartiles for the specific sample at hand. If an individual is in the highest quartile of the sample, they are coded as a one for that biomarker. Otherwise, they get a zero. These tallies were then summed up to create the allostatic load composite, which can range from zero to fifteen. Higher scores indicate more cumulative wear and tear on the body. The fifteen biomarkers I included are as follows:

- Neuroendocrine
    1. Cortisol (urine ug/dL)
    2. Norepinephrine (urine ug/dL)
    3. Epinephrine (urine ug/dL)
    4. DHEA-S (blood ug/dL)
- Cardiovascular
    1. Heart rate

2. Systolic blood pressure
3. Diastolic blood pressure

- Immune
    1. C-reactive protein (blood ug/mL, can also be considered a cardiovascular marker)
    2. Fibrinogen (blood mg/dL, can also be considered a cardiovascular marker)
    3. Serum MSD Interleukin-6 (blood pg/mL)
    4. Serum MSD Tumor necrosis factor – alpha (blood pg/mL)
- Metabolic
    1. Hemoglobin A1c (blood %)
    2. Total cholesterol (blood mg/dL)
    3. HDL cholesterol (blood mg/dL)
- Anthropometric
    1. Waist-hip ratio

Cardiovascular Disease. The presence of cardiovascular disease was self-reported with a single yes/no question, "Have you ever had heart trouble suspected or confirmed by a doctor?" For the present analyses, data were included from time 3.

Cancer. Cancer was also self-reported with a simple yes/no/don't know question, "Have you ever had cancer?" For the present analyses, data were included from time 3.

Chronic Conditions. Participants filled out a checklist asking them to mark yes/no if they have experienced various chronic conditions in the past 12 months. The list includes 39 different conditions, such as asthma, autoimmune disorders, recurring stomach trouble, etc. All of the yes answers were then summed to give a total score. For the present analyses, data were used from time 3.

Covariates. Control variables observed at time 1 that were assessed for the present study are age, gender, race, education, smoking status, alcohol abuse, and drug abuse. HIV status was considered as a potential covariate, however only one individual reported being HIV+, so it did not make sense to include in the inferential model. Alcohol and drug problems were assessed using a shortened version of the Michigan Alcohol Screening Test (Selzer, 1971). The scale contains five items and asked about problems in the past 12 months. For example, "Did you find that you had to use more alcohol than usual to get the same effect or that the same amount had less effect on you than before?" If a participant said yes to four or more items, they were scored as 1=*participant has an alcohol problem*, otherwise they were scored 0=*does not have a problem*. The same scale was used to assess drug use, except the word alcohol was substituted with substances.

Procedure

Between 1995-1996, participants were initially invited to take part in the study when a researcher randomly called their home phone number (Brim et al., 2019). The researcher would conduct a 30-minute interview to gather demographic data and determine if the participant was eligible. After that was completed, the participant would receive survey materials by postal mail. The mailings contained two packets of self-administered questionnaires. The questionnaires were long, containing about 50 pages of questions each. Beyond the specific scales mentioned in this dissertation, the MIDUS asks about numerous different personality traits, various sources of life stress, childhood history/ upbringing, social support connections, health risk/ promoting behaviors, and a wide array of self-reported mental and physical health conditions/ symptoms (Brim et al., 2019).

Data collection for time 2 was intended to fall approximately 10 years after the study began, and was carried out between 2004 and 2009 (Ryff, Seeman, & Weinstein, 2018). All participants who completed time 1 were eligible to participate in time 2, however the research team was only able to obtain working contact information for 70% of the original sample. The procedure for subsequent time points was very much the same as Time 1. Researchers conducted 30-minute phone interviews with the participants to update any changes to sociodemographic characteristics, and then they were mailed the same packet of self-administered questionnaires. Wave 2 of the MIDUS also included several different offshoot projects, for which sub-sets of the core sample were invited to participate in. The offshoot projects included a daily diary study, cognitive battery, neuroimaging study, and of course, the biomarker study. The only pre-requisite for participating in an offshoot project is that the participant had to have completed the phone interview and self-administered survey questionnaires first (Ryff, Seeman, & Weinstein, 2018).

The biomarker study required participants to travel to one of only three available clinic sites in the United States. They were required to spend two full days at the clinic. A medical professional gave the participants complete physical exams, and a trained interviewer asked them for a more detailed medical history than what is gathered with the surveys. Vital signs, such as heart rate and blood pressure were recorded. While at the clinic, participants' urine was collected in a jug and immediately handed over to a nurse each time the person used the restroom over a 12-hour period. This is done because some biomarkers, like cortisol, rise and fall after awakening and before going to bed on a diurnal rhythm. The 12-hour urine capture reflects the overall levels throughout the day. Blood draws were taken at around 7:00 am after the participants had been fasting. Complete details for how the specimens were stored and assayed by the lab can be found in the MIDUS documentation (Ryff, Seeman, & Weinstein, 2018).

Core data collection for time 3 occurred between 2013 and 2015, lining up to be about 20 years after the study began (Ryff et al., 2017). Anyone who completed the phone screening and self-administered questionnaire at time 2 was eligible to participate in time 3. Time 3, again, involved a 30-minuted phone interview and two 50-page long surveys. Additionally, time 3 is also going to include several offshoot projects, including biomarkers, but that data is not yet available. Collection for the subsidiary projects began in the latter part of 2016 and is still ongoing (Ryff et al., 2017).

Data Analysis Plan

A simplified path diagram illustrating the hypotheses is presented in Figure 2. I hypothesized that the sexual minority group will report more cardiovascular disease, more cancer, and more chronic conditions compared to the heterosexual group. I hypothesized that experiencing more everyday discrimination will lead to greater allostatic load 10 years later, and that in turn, people with high allostatic load will have developed more health problems at the next follow-up than people with lower allostatic load scores. A structural equation modeling approach was appropriate because of the multi-variate nature and complex relationships of my hypotheses. Building a large number of separate regression models to test all of the relationships would significantly raise the Type I error rate due to making so many multiple comparisons. Structural equation modeling avoids this by simultaneously testing all the different pathways together as one conglomerate set of equations.

To be explicitly clear, I did not set out to test changes in intra-individual variability, or within-person development over time. The intent of this dissertation was not to study how John Doe's cardiovascular symptoms start at baseline and observe the trajectory of that slope over each passing year. However, using longitudinal data here was still valuable because it allows me

to examine temporality of the variables. One of the most fundamental principles of epidemiology is temporality- that the cause must occur in time before the effect does. Mediation analysis is, by definition, a chain of causal pathways, and yet most mediation studies are limited by cross-sectional data where all of the variables are observed concurrently. This limitation leaves open for question whether the direction of the relationship really is that proposed, or if perhaps the outcome actually precipitates the predictor. Without establishing when they manifest, there is no way to be sure of the direction. I have removed the uncertainty around temporality by testing a sequential mediation in which everyday discrimination was measured in time before the biomarkers, and biomarkers measured well in time before the health outcomes. For the reader's curiosity though, descriptive statistics were obtained of all the outcome variables at all time points since the data is available.

Additionally, while the exact incubation period from exposure to minority stress and manifestation of disease is not known yet, 10-year spacing between waves is reasonable. The youngest individuals entering the MIDUS study at baseline are 25 years-old. Looking ahead 10 years, Crimmins and Seeman (2004) reported that differences in allostatic load scores for at-risk groups are most pronounced between the ages of 35-65. After that, we also know that the average age of first heart attack is 65 for men and 72 for women (AHA, 2015). Therefore, it seems that the time gaps between waves should be long enough to allow for the gradual effects of chronic minority stress to build up.

Before testing the actual path model, the covariates were addressed using propensity matching, following the guidelines suggested by Randolph, Falbe, Kureethara Manuel, and Balloun (2014). Propensity matching was chosen because of how imbalanced the sexual minority and heterosexual groups are. Propensity matching mitigates some of this balance by statistically

selecting a sub-set of controls from the heterosexual who are most similar to the individuals in the sexual minority group based on their covariates. The algorithm simplifies the process by boiling down all of the different covariates into just one number, the propensity score. This is much easier than a human being trying to go through a spreadsheet and trying to match two people based on age and gender, but then realizing their education doesn't match, having to throw the match out, and keep on scanning for someone else who does match. Propensity matching analyses were conducted using the R MatchIt package, specifying a 10:1 nearest neighbor match. The nearest neighbor method chooses controls based on minimizing the distance score, a measure of how much they diverge in their covariate scores from their match (Randolph et al., 2014).

Next, to test my hypotheses, I built up a series of nested models, comparing model fit at each step, until the full path diagram was represented. Analyses were conducted using Mplus Version 7 software. The first model included only one exogenous variable, sexual orientation, with the three outcome variables, cardiovascular disease, cancer, and chronic conditions regressed on it. For the second model, I added in the additional predictor variables, everyday discrimination and allostatic load, but tested for direct effects only. In the third model, all of the mediation paths were constructed, along with tests for the indirect effects.

In order to test mediation, I used the product of coefficients method rather than the traditional Baron and Kenny (1986) method. The Baron and Kenny (1986) method suffers from a number of limitations. The first is that it does not allow for the possibility that X has no direct relationship at all Y, but that it does have significant indirect effects. Their approach says that if that path is not significant, stop and don't bother doing any further testing. Another limitation with their method is that it can only tell you if mediation is significant or not; it cannot quantify

the magnitude of the relationships. A final limitation with the Baron and Kenny (1986) method is that is has been shown to be lacking in statistical power, thus making researchers more likely to commit a Type II error (Fritz & MacKinnon, 2007).

Hayes (2009) explains that the magnitude of the indirect effect can be quantified; its equation is given by a*b = c – c'. (The a*b term is where the technique gets its name, product of coefficients.) Hayes (2009) further argues that we should not be relying on the Sobel test to test for significance of the indirect effect, a statistic that assumes normality, when the indirect effect is almost never normally distributed. Instead, bootstrapping or simulation methods should be used to estimate confidence intervals. If the interval does not overlap zero, we can be 95% confident that the strength of the indirect effect is not zero.

Instead of the Sobel test, bias-corrected bootstrapped confidence intervals were used to test the significance of the indirect effects. Unlike regular confidence intervals, the bias-corrected ones are allowed to be asymmetrical, and thus account for the non-normality of the product term. This approach works by treating the observed dataset as the "population" and drawing a new random sample from it (with replacement) many times. After repeating this process many times, a new sampling distribution is constructed, whose shape determines where the lower and upper bounds of the confidence interval falls. Hayes and Scharkow (2013) conducted simulation tests of indirect effects and declared the Sobel test the least trustworthy, and bias-corrected bootstrapped confidence intervals having the most power.

At each step, I examined how model fit changed with the inclusion of new parameters. Model fit was evaluated using the criteria set by Hu and Bentler (1999). They recommend that for excellent fit, the Comparative Fit Index and Tucker-Lewis Index should both exceed .95. For acceptable fit, they should exceed .90. The root mean square error of approximation (RMSEA)

and the weighted root mean square residual (WRMR) should be below .08 for excellent fit, and .10 for acceptable fit (Hu & Bentler, 2009). Model fit was also evaluated using chi-square values. Smaller chi-square values indicate better model fit. If model fit does not improve noticeably with the inclusion of a new parameter, that parameter is not helping to better explain variance and should be considered for removal. This iterative model building process helps researchers to settle on the most parsimonious model.

Power Analysis

I conducted a power analysis a priori using Mplus Version 7. Because the sample size is constrained by the fact that the data has already been collected, the purpose of the power analysis was to determine if the model I proposed is even worth testing (or might need to be simplified), rather than to determine target sample size. I followed the guidelines outlined by Thoemmes, MacKinnon, and Reiser (2010), who document step by step how to estimate power in complex mediation designs within a SEM framework. To achieve this, Mplus uses Monte Carlo simulations of the model that the researcher specifies. The researcher sets up the syntax specifying all of the paths (relationships among variables) exactly as they would if they were actually analyzing the real data, with the only difference being that they define plausible starting values for the different parameters to be estimated. I chose to take a conservative approach and specified small effect sizes for all the paths, starting the regression coefficients at 0.3. I did this because there is relatively scant literature on sexual orientation and allostatic load to take cues from in selecting plausible values, and because a few of those studies that do exist have found small group differences that were on the cusp of significance, but not quite there. Small effect sizes require larger samples to be able to detect, and thus more power.

Monte Carlo simulations work by having the computer generate artificial "population data" that fits the constraints the researcher specified. Then, it draws a random subset of that artificial data with the sample size specified. Next, it runs the actual analytical model on that artificial sample data. The computer records whether or not each parameter was found to be statistically significant. It repeats this process many times over, tallying up how many runs were found to be significant for each parameter out of how many total runs were conducted. Generally, in the social sciences, this benchmark is set to be 80% power. All of the parameters of interest should come up as significant in 80 out of 100 trial runs. In my power analysis, I asked for 10,000 iterations or trial runs. Several hundred is considered the minimum limit, but Thoemmes et al. (2010) recommend 10,000 as an optimal number. I set the requested sample size to be 495 since I already know how much data I have access to. If one did not already know how much data was available, they would repeat the power analysis several times, altering only the sample size. The researcher would decrease the requested sample size each time, and using trial and error, keep going until they found the threshold where power for all of the parameters drops below 80%. That threshold is the minimum required sample size to pursue the study.

In running this power analysis, I discovered that my model would have 99% power to successfully detect my hypothesized relationships (both direct and indirect effects), which is reasonable given what other researchers have found. Thoemmes et al. (2010) demonstrated the Monte Carlo technique using two intervening mediators, like with the model I hypothesized, medium effect sizes, and sample size set to only $n = 90$. With that, they found they had 95% power to detect the direct effects, and 53% power to detect indirect effects. In a different illustrative example, Fritz and MacKinnon (2007) specified only one mediator variable and varying effect sizes. For a small effect size ($b = 0.26$) they determined that a sample size of $n =$

161 would be needed to achieve 80% power. These published pedagogical examples aren't perfect apples to apples comparisons of the exact model I have specified, but they give the reader a general sense of what a plausible range looks like for mediation models.

RESULTS

Propensity Matching

The first step of a propensity matching analysis, checking the common support assumption, was done by plotting a histogram of the propensity scores, shown in Figure 3. The common support assumption requires that there be at least some overlap in the propensity scores of the two groups. If there is no overlap, it suggests the groups are fundamentally different from each other in their covariates and cannot be reasonably assumed to be from the same underlying population (Randolph et al., 2014). The areas in Figure 3 that include both stripes and gray shading are the areas where the sexual minority and heterosexual groups overlap.

Having met this assumption, the analysis was deemed appropriate and matches were selected. New histograms were constructed, comparing the groups before and after matching. These are presented in Figure 4. These graphs show that with the raw data, the heterosexual control group's propensity scores skewed lower. After matching, the distribution of the propensity scores much more closely resembles the shape of the sexual minority group's distribution.

To check the quality of the matches drawn, the mean differences between the groups on all covariates were calculated before and after matching. These are presented in Table 3. After matching, mean difference scores should be as close to zero as possible (Randolph et al., 2014). The balance improvement exceeded 80% for all covariates, except for race and alcohol abuse. Those two variables had the lowest mean difference scores to begin with, so it could be that there was a ceiling on how much room for improvement was possible. This new matched dataset (n =

495) is what was used in all other analyses. Demographics were recalculated and broken out by the sexual minority vs. heterosexual groups. These are presented in Table 4.

Descriptive Statistics

Descriptive statistics for the main study variables of interest are presented in Table 5. Across all time points, the sexual minority group reported more everyday discrimination and more chronic conditions than the heterosexual group. Higher allostatic load scores were also observed in the sexual minority group compared to the heterosexuals, which was only observed at time 2. With regard to cancer, the heterosexual group actually had slightly higher rates across all time points, about 1.5% more than reported in the sexual minority group. For cardiovascular disease, the sexual minority group started off with noticeably higher rates at time 1, but by time 3 frequencies were very similar to the heterosexual group.

Path Models

The first path model tested the significance of group differences only by regressing the main study variables on sexual orientation. Fit statistics are presented in Table 6, and all were in the excellent range. This model revealed that sexual minorities scored on average 1.45 points higher on everyday discrimination ($\beta = 1.45$, $SE = .60$, $p = .02$). The coefficient for allostatic load was not statistically significant, indicating that the mean difference observed between the two groups was not large enough to be meaningful. Additionally, there were no significant differences for cancer or cardiovascular disease. Sexual minorities did report significantly more chronic conditions than did heterosexuals ($\beta = 1.21$, $SE = .42$, $p = .004$). All coefficients for this model are summarized in Table 7.

The second path model set up all of the direct effects, regressing the three outcome variables on sexual orientation, everyday discrimination, and allostatic load. This model did not

yet introduce the indirect effects or bootstrapping. Model fit did not change with the inclusion of the new paths, and these values are again reported in Table 6. None of the direct effects were significant for cancer or cardiovascular disease. However, all of the direct effects for chronic conditions were significant. A greater number of chronic conditions was significantly predicted by being a sexual minority (β = 1.04, *SE* = .42, *p* = .014), higher discrimination scores (β = .09, *SE* = .03, *p* = .004), and higher allostatic load scores (β = .14, *SE* = .05, *p* = .003). All coefficients for this model are summarized in Table 8. The paths for chronic conditions are also illustrated in Figure 5.

The final path model represents the complete set of mediation hypotheses and includes all indirect effects with bias-corrected bootstrapped confidence intervals. Once again, no significant differences were found for cancer or cardiovascular disease. Regarding chronic conditions, mediation was mostly supported. The a path (X: sexual orientation > M1: everyday discrimination), which was previously significant, became no longer significant, (β = 1.45, *SE* = .78, *p* = .06). The first b path (M1: everyday discrimination > M2: allostatic load) was not significant (β = .03, *SE* = .02, *p* = .15). The second b path (M2: allostatic load > Y: chronic conditions) was significant, indicating increased allostatic load is associated with more chronic conditions (β = .14, *SE* = .07, *p* = .04). Finally, the c' path (X: sexual orientation > Y: chronic conditions) was also significant, indicating that sexual minorities still had more chronic conditions even when controlling for the two mediators (β = 1.04, *SE* = .51, *p* = .04). The overall indirect effect going from X: sexual orientation > M1: everyday discrimination > M2: allostatic load > Y: chronic conditions was significant (Total = .007, 95% CI [0, .04]). While the absolute magnitude appears small, this is expected when multiplying fractions. All coefficients for this model are reported in Table 9 and further illustrated in Figure 6.

DISCUSSION

The present study hypothesized that sexual minorities would experience higher rates of cancer, cardiovascular disease, and chronic conditions compared to heterosexuals. It was further hypothesized that those effects would be mediated sequentially via everyday discrimination and allostatic load. This was the first study (to my knowledge) to test a complete mediation model linking sexual minority stress to physical health outcomes, and to have observed the variables prospectively. Hypotheses for cancer and cardiovascular disease were not supported. This finding contradicts existing research, which has found significant differences in cancer (Koblin et al., 1996; McNair et al., 2011), and cardiovascular disease (Boehmer et al., 2014; Diamont & Wold, 2003; Roberts et al., 2003; Case et al., 2004; Conron et al., 2010) by sexual orientation.

One reason for the disparate finding with regard to cancer could be that the present study asked about any kind of cancer, while previous research has identified differences in specific types of cancer, such as anal, breast, and non-Hodgkin's lymphoma (Koblin et al., 1996; McNair et al., 2011). Higher rates in those specific cancers could be attributable to other risk factors that sexual minorities possess. Anal cancer develops from HPV, a sexually transmitted disease, which gay men are at higher risk for (American Cancer Society, 2018). Likewise, non-Hodgkin's lymphoma can be an AIDS-related illness. It could be that sexual minorities are only at increased risk for certain cancers that are attributable to these other risk factors, and not that they are universally at higher risk for any kind of cancer. More research would be needed comparing rates of other types of cancer that could not be conceivably tied to other sexual minority risk factors to verify if this is the case.

Regarding cardiovascular disease, one factor the present study was not able to assess was the age of onset for heart problems. One study that did examine this found no differences in cardiovascular disease by sexual orientation among older adults, but did find differences for people under 40 (Boehmer et al., 2014). The under-40 sexual minorities were at roughly 3 times the risk (odds ratio for lesbians: 3.71, odds ratio for gay men 2.78). Looking for signs of premature aging may be just as important as measuring prevalence rates for capturing the overall burden of disease in the sexual minority population.

For chronic conditions, all of the direct effects were supported. Being a sexual minority, experiencing more everyday discrimination, and having a higher allostatic load score were all significantly associated with having more chronic health conditions. The indirect effect was also supported, indicating that chronic conditions are transmitted via discrimination and allostatic load. When looking at the individual paths within the mediation model, not all of them were significant. There could be room to improve upon the operationalization of these constructs to better refine the path model.

For example, one area that could be improved upon is that the present study had to use everyday discrimination as a proxy variable for the operationalization of minority stress. Minority stress is a multi-faceted construct that is comprised of numerous factors: discrimination events, victimization events, rejection anticipation, identity concealment, internalized stigma, as well as everyday discrimination (Meyer, 2003). While all of those dimensions have been associated with poorer mental health outcomes (Meyer, 2003), it less clear how physical health outcomes may differ based on which minority stress dimensions are assessed, or which areas an individual scores higher on. Comprehensive studies that measure all of the minority stress dimensions against biomarker data are needed to fully deconstruct those relationships, but

acquiring such data will be difficult. Large national studies do not have space in their surveys to add dozens of additional items representing all the components of minority stress, while individual researchers have limited resources for collecting costly biomarker specimens.

Another way the mediation model could potentially be improved is by assessing appraisal of the stressor instead of exposure. For example, instead of asking how frequently a person has experienced everyday discrimination, ask them how upsetting they perceived those situations to be. This recommendation stems from Lazarus and Folkman's (1987) foundational theoretical work in the stress field, which says that stressors must be perceived as harmful or threatening in order for them to impact wellbeing. There is some longitudinal work that supports the link between appraisal and longer-term health outcomes. Caregivers of spouses with dementia who appraised their caregiving activities as more negatively had developed more physical health symptoms themselves one year later than those who did not appraise the task as severely (Goode, Haley, Roth, & Ford, 1998). Another study found that medical students who displayed "frail" appraisal profiles in response to common life stressors had significantly worse physical well-being years later than did the students who showed "resilient" appraisal profiles (Hojat, Gonnella, Erdmann, & Vogel, 2003).

If one were to assess appraisal in the context of sexual minority stress, there are tradeoffs that must be considered with regards to how to measure it. Self-report scales are a common way to assess appraisal. For example, in the caregiving study, Goode et al. (1998) asked two follow-up questions for each caregiving activity the respondents endorsed: How stressful did they perceive the problem to be and how confident did they feel in managing the problem? A similar approach could be implemented by offering survey takers a checklist of sexual minority stressors and piping in the two follow-up questions for all items endorsed. Such a self-report tool would

be affected by recall bias to some degree though. Some sexual minority stressors are infrequently occurring events (e.g. being fired from a job or given improper medical care) and thus may require a respondent to think backwards many months or years in time.

An alternative approach that would not suffer from recall bias would be to implement an experimental design. Such an approach would involve inviting participants to a laboratory and intentionally exposing them to a stressor (e.g. have a confederate make an anti-gay remark in the waiting room, leave a radio clip playing in the background of a politician with anti-LGBT policies.) The benefit of this approach is that the researcher could measure immediate affective and physiological reactions to the stressor. The major limitation to such a design is that it would only allow one to draw conclusions about acute reactions to stress, thus neglecting a core tenet of sexual minority stress theory, which says that it is a chronic life-long form of stress (Meyer 1995; 2003). These limitations present challenges for researchers wishing to study appraisal in sexual minority populations.

In additional to appraisal, another factor that deserves consideration is disclosure. Because the MIDUS is not a fully anonymized study, and especially the biomarker portion of it, which requires filling out forms that will be turned over to the healthcare workers face to face, it is reasonable to assume that the participants have at least partially disclosed their sexual orientation. This factor is relevant because minority stress theory says that identity concealment is one of the dimensions of minority stress that contributes to worse outcomes (Meyer, 2003). It is possible that the sexual minority MIDUS participants had better outcomes than not-represented fully undisclosed sexual minority individuals. This could partially explain why my results showed that sexual minorities did have higher allostatic load scores than heterosexuals, but that difference did not rise to the level of statistical significance. Some preliminary evidence

on disclosure and health supports this possibility. Juster et al. (2013) found that sexual minorities who disclosed their orientation to the researchers but reported not being disclosed to family and friends had significantly higher wakening cortisol levels than fully out individuals.

Yet another LGBT-specific consideration that warrants further research is what effect geographic region has on allostatic load and other physical health outcomes. Hatzenbuehler, Keyes, and Hasin (2009) compared LGBT participants who lived in protective versus non-protective states. States were classified based on whether they included sexual orientation in the definition for hate crimes, and whether they banned employers from discriminating on sexual orientation. Individuals living in non-protective states had higher rates of anxiety, PTSD, and dysthymia (Hatzenbuehler et al., 2009). In a separate study, Hatzenbuehler, McLaughlin, Keyes, and Hasin (2010) tracked sexual minority respondents before and after many states implemented in gay marriage bans. Individuals living in states that enacted bans reported significant upticks in mood disorders, anxiety, and alcohol use (Hatzenbuehler et al., 2010).

Less is known about how differences by region in legislation, public attitudes, healthcare resources, and access to like-minded communities impact physical health outcomes for sexual minorities. In the general population, people living in rural areas are at higher risk for death from heart disease, cancer, stroke, injury, and respiratory disease compared to urban dwellers (CDC, 2017). It is plausible that the disparity between urban and rural for physical health is amplified in the LGBT population. Unfortunately, the MIDUS does not report individual participants' place of residence so such differences could not be examined in this dissertation.

The present study is not without its limitations. One challenge is that the sample was heavily unbalanced to have many more heterosexual participants. While the overall percentage of LGB participants (4.76%) is representative of the general U.S. population, in which

approximately 4.5% are estimated to identify as a sexual minority (Newport, 2018), it does leave statistical tests for that group under-powered relative to the much larger sample size the heterosexual group has. Researchers wishing to study sexual orientation may need to intentionally oversample this group to address the imbalances in statistical power.

Additionally, because this was a longitudinal study, another potential limitation is the impact of cohort effects. The entire sample was coming into middle age in 1995 when data collection first began. The MIDUS cohort is especially unique because of the drastic changes in the social landscape for the LGBT population in the United States that occurred over the timespan of 1995-2015 when data collection took place. For older generations, attitudes about homosexuality were relatively flat, hovering between 10-15% approval from 1970 – 1993 (Fetner, 2016). A shift in attitudes occurred though in 1993, where approval steadily climbed upward, reaching almost 50% by 2015 (Fetner, 2016). In subsequent generations, attitudes go back to being mostly flat, albeit positive. Today, only 15% of Millennials and Gen Z say gay marriage is bad for society (Parker, Graf, & Igielnik, 2019).

Mirroring the changes in public opinion, significant legislative changes occurred during the MIDUS data collection period as well. The Defense of Marriage Act, banning same-sex marriage, was passed in 1996 and then repealed in 2013. Similarly, Don't Ask Don't Tell, the policy blocking service members of the military from coming out as LGBT, was passed in 1994 and then repealed in 2011. The particular sociopolitical environment that the MIDUS cohort aged in may be a one-time only historical event. It seems unlikely that any other cohort will experience fluctuations in public attitudes towards sexual minorities as extreme as what occurred between 1995-2015.

Another consideration for the present research is with regards to how allostatic load is operationalized. This dissertation measured allostatic load as a sum of how many biomarkers are abnormally high (in the worst quartile). New and alternative ideas have been put forth though for how to best represent physiological functioning. One such idea is the reactivity hypothesis, which says that the more variation a person exhibits from resting baseline to immediately following an acute stressor, the more they are at risk for developing future cardiovascular disease. In recent years, new evidence has come out challenging the reactivity hypothesis. This evidence suggests that both overreacting to and underreacting to stress are maladaptive for health. The strongest evidence for this has been found with regards to cortisol reactivity. Numerous studies have found an association between blunted cortisol reactivity after an acute lab stressor and psychiatric disorders (Zorn et al., 2017).

Some studies are beginning to find this pattern with other biomarkers too, such as decreased alpha amylase (Altamura et al., 2018), DHEA and DHEA-S (Jiang et al., 2017), diminished prefrontal-amygdala functional connectivity (Ottaviani, 2018), and less heartrate variability (Souza et al., 2015). These findings raise questions about what we conceive of as normal/ healthy biomarker thresholds. Should measures of allostatic load be two-tailed, looking for both abnormally low and high values? Similarly, while minority stress theory emphasizes the chronic ongoing nature of exposure to sexual minority stress, from a physiological perspective, would it make more sense to measure what a person's pattern of responding to typical acute minority stressors in the moment is? Perhaps knowing whether an individual exhibits blunted, about average, or heightened reactivity to the small, individual minority stressors that come up day to day would have more utility in predicting what their long-term health outcomes will be.

One final idea to consider is the theme of resiliency. Meyer (2003) says that sexual minority individuals can build resiliency by gaining social support and group-level resources from their communities. Likewise, Epel, McEwen, and Ickovics (1998) posit that the body can exhibit a physiological profile of resiliency, indicating the person is growing and thriving in response to stress. For a healthy person, the parasympathetic nervous system should activate the release of anabolic hormones (growth hormone, insulin-like growth factor IGF-1, and insulin) after a stress response to return everything back to normal. The authors state that physiological resilience can be measured by the ratio of anabolic to catabolic hormones. A higher ratio of anabolic hormones indicates a person has adapted to stress and is equipped to handle future stress. Equal levels indicate what we might think of as an overly sheltered person – their health is unaffected because they haven't experienced much stress, but they also haven't had the opportunity to grow stronger by learning to manage challenges. A higher ratio of catabolic hormones indicates disease (Epel et al., 1998). Instead of only looking for where things have gone bad across the body, as was done in the present study and most studies of allostatic load, future research may instead consider looking for the balance of specific matched biomarkers.

In conclusion, this was the first known study to test a complete mediation model connecting minority stress to biomarkers to physical health outcomes. The results suggest that everyday discrimination and allostatic load are meaningful predictors of health outcomes for the sexual minority population, as evidenced by significant direct effects. They alone are not enough to fully explain health disparities though. Sexual orientation continued to be a significant predictor, even after controlling for the two mediators. This study was an important first step for identifying the mechanism by which a chronic life-long psychosocial stressor, sexual minority stress, manifests as numerous different physical health disparities.

Table 1

Biomarker Studies with Sexual Minority Samples

First Author	Dataset	Covariates	HR	BP	W/H	BMI	Cort	NorE	Epi	DHEA-S	CRP	Fib	IL-6	TNF	Alb	A1c	Chol
Used for present study	MIDUS I, II, III	Age, sex, race, education, smoking, alcohol abuse, drug abuse, HIV status	x	x	x		x	x	x	x	x	x	x	x		x	x
Arheart (2013)	NHANES 2005-10	Age, sex, race, education	x	x		x					x				x	x	x
Caceres (2018)	NHANES 2001-12	Mental distress, smoking, binge drinking, exercise, dietary fat		x		x										x	x
Clark (2015)	Add Health	Age, race, education, financial distress		x		x										x	
Doyle (2016)	Community sample (n=99)	Alcohol use, medication, race, age				x							x				
DuBois (2017)	FTM on testosterone (n=65)	Time on testosterone, steroid use, cortisol awakening response				x	x										

First Author	Dataset	Covariates	HR	BP	W/H	BMI	Cort	NorE	Epi	DHEA-S	CRP	Fib	IL-6	TNF	Alb	A1c	Chol
Everett (2014)	Add Health	Age, race, education, hormone therapy				x					x						
Farmer (2013)	NHANES 2001-10	Race, education, income, drug & alcohol use, family history of CVD		x		x											x
Glover (2013)	Black HIV+ MSM (n=99)	Age, smoking, drug use, time since diagnosed. Additional biomarkers: neopterin, dopamine		x	x	x	x	x	x								
Harper (2016)	Add Health	Age, education, income		x		x											x
Hatzenbuehler (2013)	Add Health	Age, race, education, income, smoking, alcohol use, exercise, medications	x	x		x					x					x	
Hatzenbuehler (2014a)	Community sample LGB young adults (n=74)	Age, sex, race, wake time, smoking, exercise, caffeine use					x										

First Author	Dataset	Covariates	HR	BP	W/H	BMI	Cort	NorE	Epi	DHEA-S	CRP	Fib	IL-6	TNF	Alb	A1c	Chol
Hatzenbuehler (2014b)	Add Health	Age, race, education, income, smoking, alcohol use, exercise, medications, illness in past 2 weeks	x	x	x						x					x	
Juster (2016)	Community sample of LGB youth (n=87)	Age	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Juster (2013)	Same as above	Age, chronic general stress	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Juster (2015a)	Same as above	Age, sex hormones, disclosure status, self-esteem					x										
Juster (2015b)	Same as above (subset, n=46)	Sex	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Krueger (2015)	Add Health	Age, race, education, income, alcohol use, smoking exercise, sleep problems, medication	x	x	x	x					x					x	x

First Author	Dataset	Covariates	HR	BP	W/ H	BMI	Cort	NorE	Epi	DHEA -S	C RP	Fib	IL-6	TNF	Alb	A1c	Chol
Mays (2018)	NHANES 2001-10	Age, race, education, foreign birth, health insurance, smoking, mental distress, exercise, HIV status, substance use	x	x		x					x				x	x	x
Parra (2016)	Community sample of LGB young adults (n=50)	Age, sex, ethnicity, language spoken					x										

Note. Abbreviations are: HR-heart rate, BP-blood pressure, W/ H- waist hip ratio, BMI-body mass index, Cort- cortisol, NorE-norepinephrine, Epi-epinephrine, DHEA –S-Dehydroepiandrosterone sulfate, CRP-C-reactive protein, Fib-fibrinogen, IL-6-interleukin-6, TNF-tumor necrosis factor, Alb- albumin, A1c- glycosylated hemoglobin A1c, Chol-cholesterol

Table 2

Demographic Variables for All Data

Group	*n*	Percentage
Total	945	100.00%
Age	45.27	(11.1)
Sexual Orientation		
Heterosexual	899	95.13%
Sexual Minority	45	4.76%
Gender		
Male	420	44.44%
Female	525	55.56%
Education		
Did not graduate high school	34	3.60%
High school diploma/ GED	222	23.49%
College	496	52.49%
Graduate School	192	20.32%
Race		
White	861	91.11%
Black	25	2.65%
Native American	3	0.32%
Asian/ Pacific Islander	2	0.21%
Multi-Racial / Other	25	2.64%
HIV Status		
Positive	1	0.11%
Negative	920	97.35%
Smoker		0.00%
No	265	28.04%
Yes	416	44.02%
Alcohol Abuse		
No	936	99.05%
Yes	9	0.95%
Substance Abuse		
No	941	99.58%
Yes	4	0.42%

Note. Mean (SD) given for age.

Table 3

Improvement After Propensity Matching

Covariate	Mean Difference Before	Mean Difference After	% Balance Improvement
Age	-4.71	-0.72	84.76
Gender	-0.16	-0.02	85.09
Education	0.08	0.00	94.67
Race	-0.06	-0.05	20.98
Smoking	0.10	0.02	81.73
Alcohol Abuse	0.01	0.01	16.60
Substance Abuse	0.00	0.00	100.00

Table 4

Demographic Variables for Propensity Matched Data

Covariate	All		Sexual Minority		Heterosexual	
	n	Percentage	*n*	Percentage	*n*	Percentage
Total	495	100%	45	9.09%	450	90.9%
Age	41.41	(10.46)	40.76	(11.39)	41.47	(10.37)
Gender						
Male	286	57.78%	27	60.00%	259	57.56%
Female	209	42.22%	18	40.00%	191	42.44%
Education						
Did not graduate high school	12	2.42%	1	2.22%	11	2.44%
High school diploma/ GED	97	19.60%	10	22.22%	87	19.33%
College	278	56.16%	23	51.11%	255	56.67%
Graduate School	108	21.82%	11	24.44%	97	21.56%
Race						
White	448	90.51%	43	95.56%	405	90.00%
Black	14	2.83%	0	0.00%	14	3.11%
Native American	2	0.40%	0	0.00%	2	0.44%
Asian/ Pacific Islander	1	0.20%	0	0.00%	1	0.22%
Multi-Racial / Other	11	2.22%	1	2.22%	10	2.22%
Smoker						
No	126	25.45%	13	28.89%	113	25.11%
Yes	256	51.72%	24	53.33%	232	51.56%
Alcohol Abuse						
No	489	98.79%	44	97.78%	445	98.89%
Yes	6	1.21%	1	2.22%	5	1.11%
Substance Abuse						
No	495	100.00%	45	100.00%	450	100.00%
Yes	0	0.00%	0	0.00%	0	0.00%

Note. Mean (SD) given for age.

Table 5

Descriptive Statistics for Outcome Variables

Variable	Time 1		Time 2		Time 3	
	Sexual Minority	Heterosexual	Sexual Minority	Heterosexual	Sexual Minority	Heterosexual
Everyday Discrimination	14.18 (5.14)	12.73 (4.27)	15.13 (5.37)	12.86 (4.42)	13.56 (5.46)	12.43 (4.17)
Allostatic Load	-	-	4.04 (2.68)	3.70 (2.25)	-	-
Cancer	2 (4.4%)	24 (5.3%)	3 (6.7%)	41 (9.1%)	7 (15.6%)	78 (17.3%)
Cardiovascular Disease	6 (13.3%)	39 (8.7%)	3 (6.7%)	60 (13.3%)	8 (17.8%)	84 (18.7%)
Chronic Conditions	2.86 (2.30)	2.04 (2.21)	2.64 (2.86)	2.05 (2.06)	4.14 (3.17)	2.93 (2.83)

Note. Mean (SD) given for continuous variables. Count (percentage) who have the condition given for binary variables.

Table 6

Fit Indices for Nested Models

Model	χ^2	CFI	TLI	RMSEA	WRMR
Sexual orientation	53 (15)*	1.0	1.0	0*	.003
Direct effects	53 (15)*	1.0	1.0	0*	.001
Final					.001

Note. *p<.05

Table 7

Model Testing Differences by Sexual Orientation Only

Outcome	*β*	*SE*	*p*	95% CI
Discrimination	1.45	(.60)	.02	[.27, 2.63]
Allostatic load	0.34	(.32)	.28	[-.28, .96]
Cardiovascular disease	-.03	(.23)	.89	[-.48, .42]
Cancer	-.07	(.24)	.76	[-.54, .39]
Chronic conditions	1.21	(.42)	.004	[.38, 2.03]

Table 8

Model Testing Direct Effects Only

Path	β	*SE*	*p*	95% CI
Discrimination				
ON Sexual orientation	1.45	.60	.02	[.27, 2.63]
Allostatic load				
ON Sexual orientation	.29	.32	.36	[-.34, .92]
ON Discrimination	.03	.02	.15	[-.01, .08]
Cardiovascular disease				
ON Sexual orientation	-.02	.23	.94	[-.47, .44]
ON discrimination	-.02	.02	.20	[-.05, .01]
ON Allostatic load	.03	.03	.26	[-.03, .09]
Cancer				
ON Sexual orientation	-.06	.24	.82	[-.53, .41]
ON Discrimination	0.0	.02	.92	[-.03, .03]
ON Allostatic load	-.05	.03	.12	[-.10, .01]
Chronic conditions				
ON Sexual orientation	1.04	.42	.014	[.21, 1.86]
ON Discrimination	.09	.03	.004	[.03, .14]
ON Allostatic load	.14	.05	.003	[.05, .23]

Table 9

Final Model Coefficients

Path	β	*SE*	*p*	95% CI
Discrimination				
ON Sexual orientation	1.45	.78	.06	[.05, 3.09]
Allostatic load				
ON Sexual orientation	.29	.40	.47	[-.43, 1.19]
ON Discrimination	.03	.02	.15	[-.02, .08]
Cardiovascular disease				
ON Sexual orientation	-.02	.24	.94	[-.53, .43]
ON discrimination	-.02	.02	.22	[-.05, .01]
ON Allostatic load	.03	.03	.22	[-.02, .09]
Cancer				
ON Sexual orientation	-.06	.26	.83	[-.60, .38]
ON Discrimination	0.0	.02	.92	[-.03, .03]
ON Allostatic load	-.05	.03	.12	[-.10, .01]
Chronic conditions				
ON Sexual orientation	1.04	.51	.04	[.05, 2.07]
ON Discrimination	.09	.03	.01	[.02, .15]
ON Allostatic load	.14	.07	.04	[.03, .29]
Indirect effects				
Cardiovascular disease	.002	.002	-	[0, .01]
Cancer	-.002	.003	-	[-.02, 0]
Chronic conditions	.007	.008	-	[0, .04]

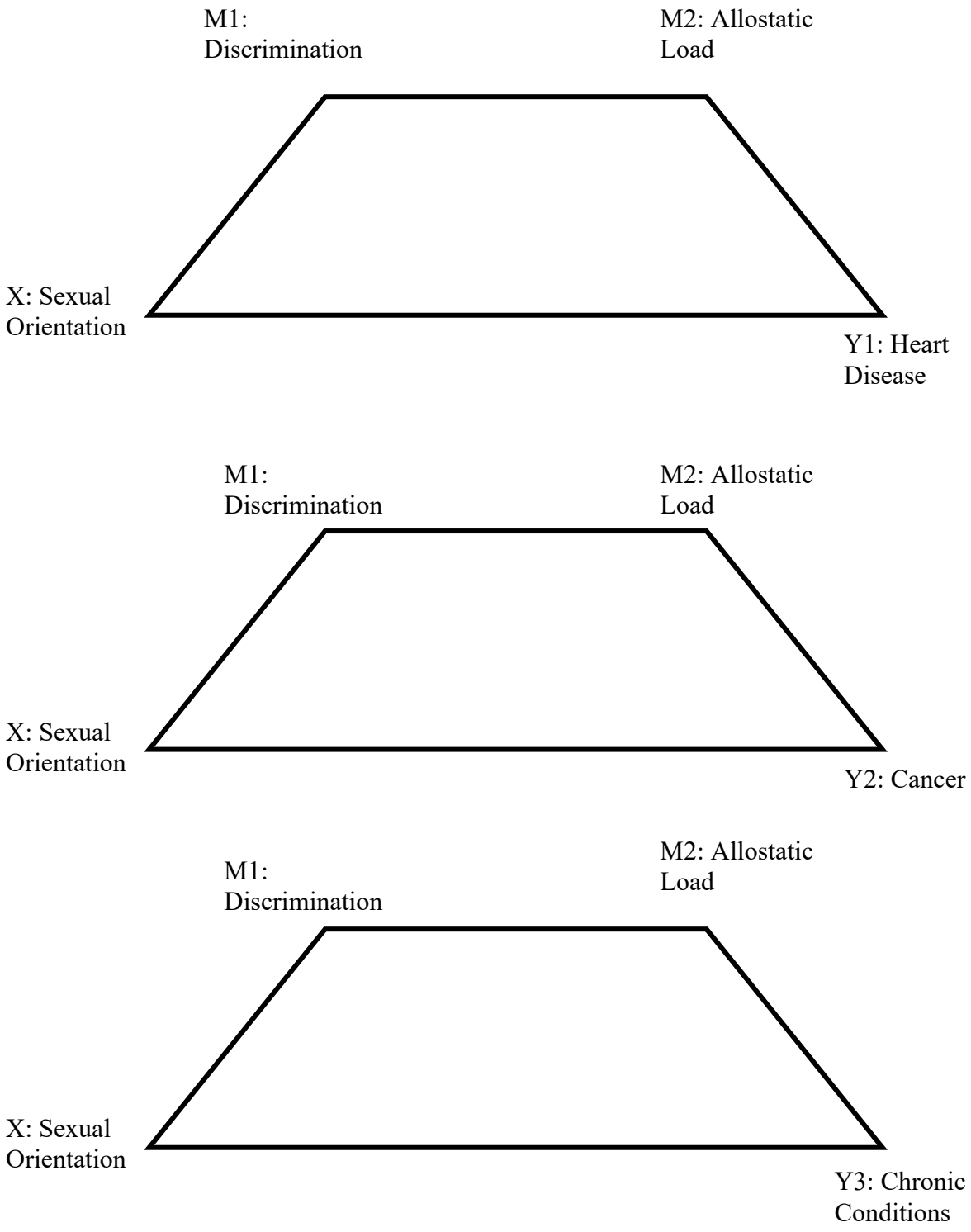

Figure 1. Simplified sequential mediation paths

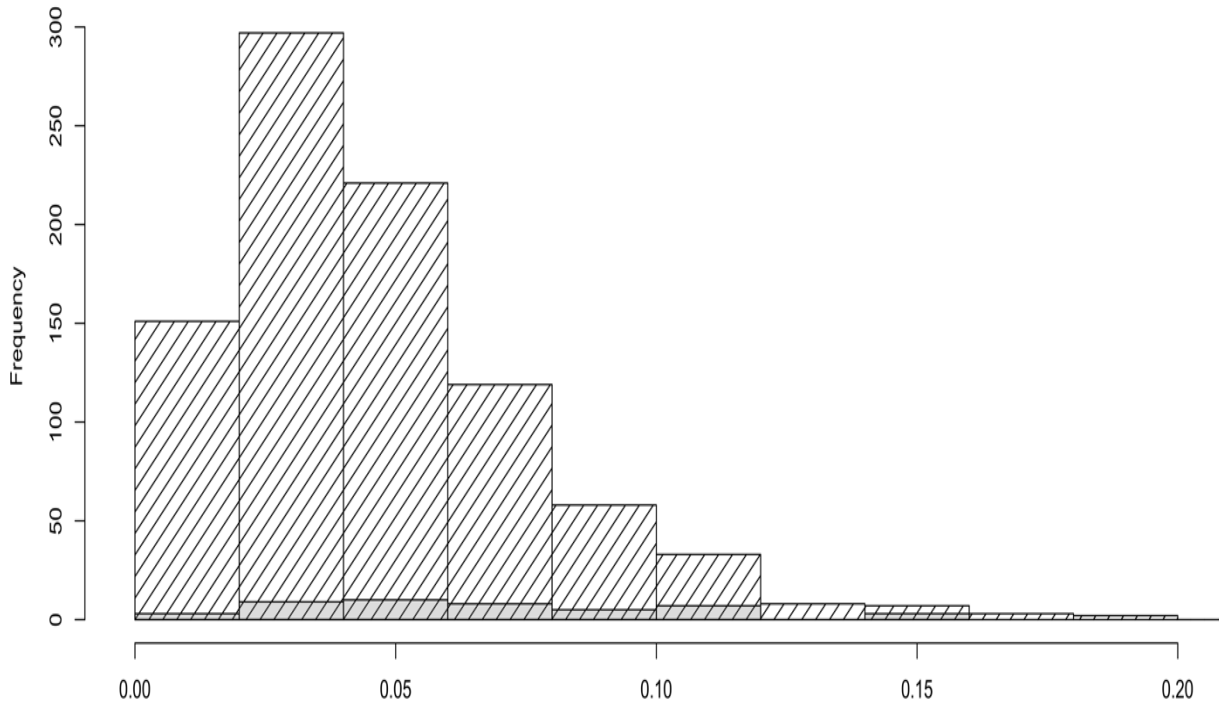

Figure 2. Common support assumption checking. The stripes are the heterosexual propensity scores and the gray shading are the sexual minority propensity scores. The regions overlap, so the assumption is met.

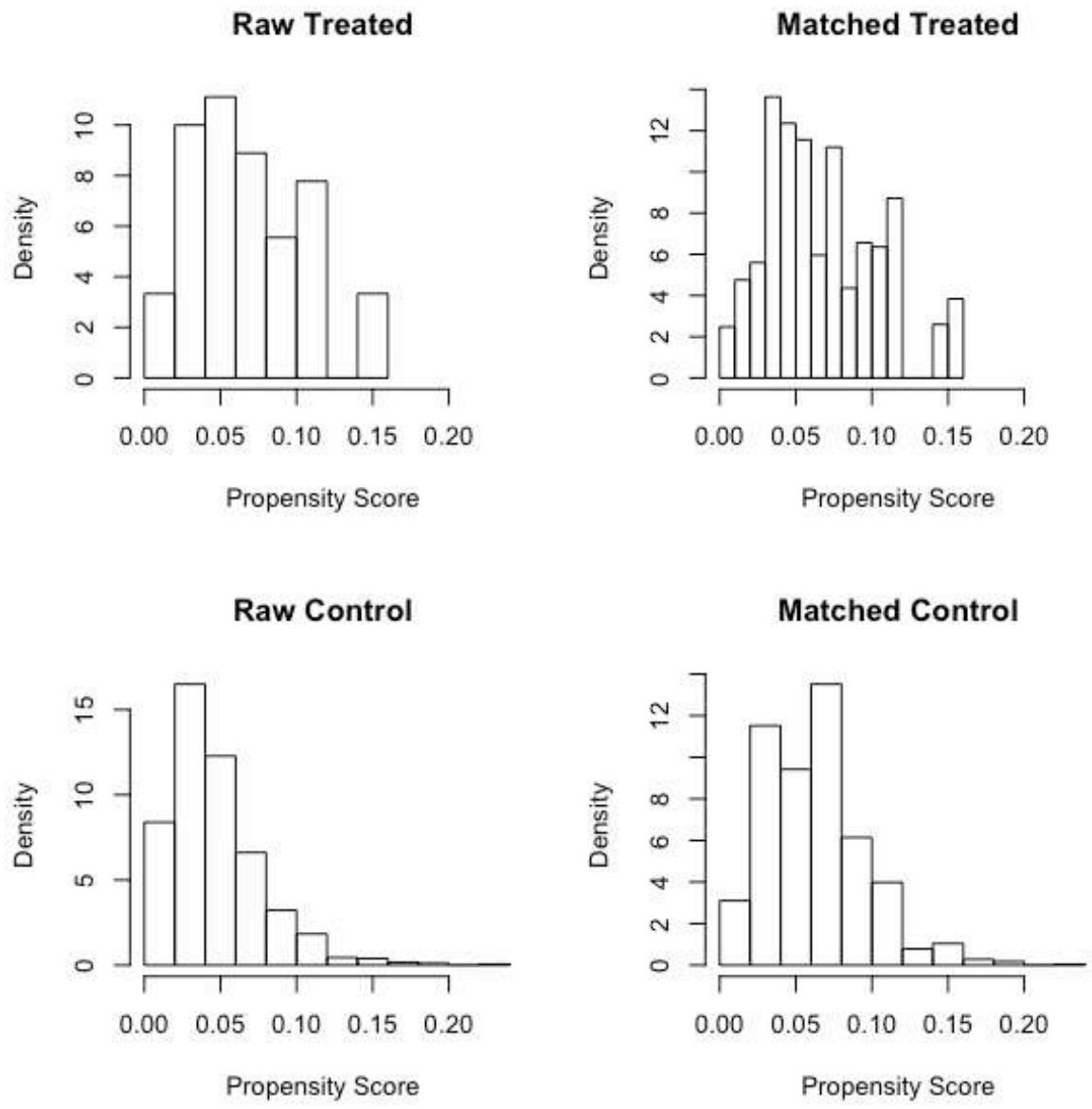

Figure 3. Distribution of propensity scores before and after.

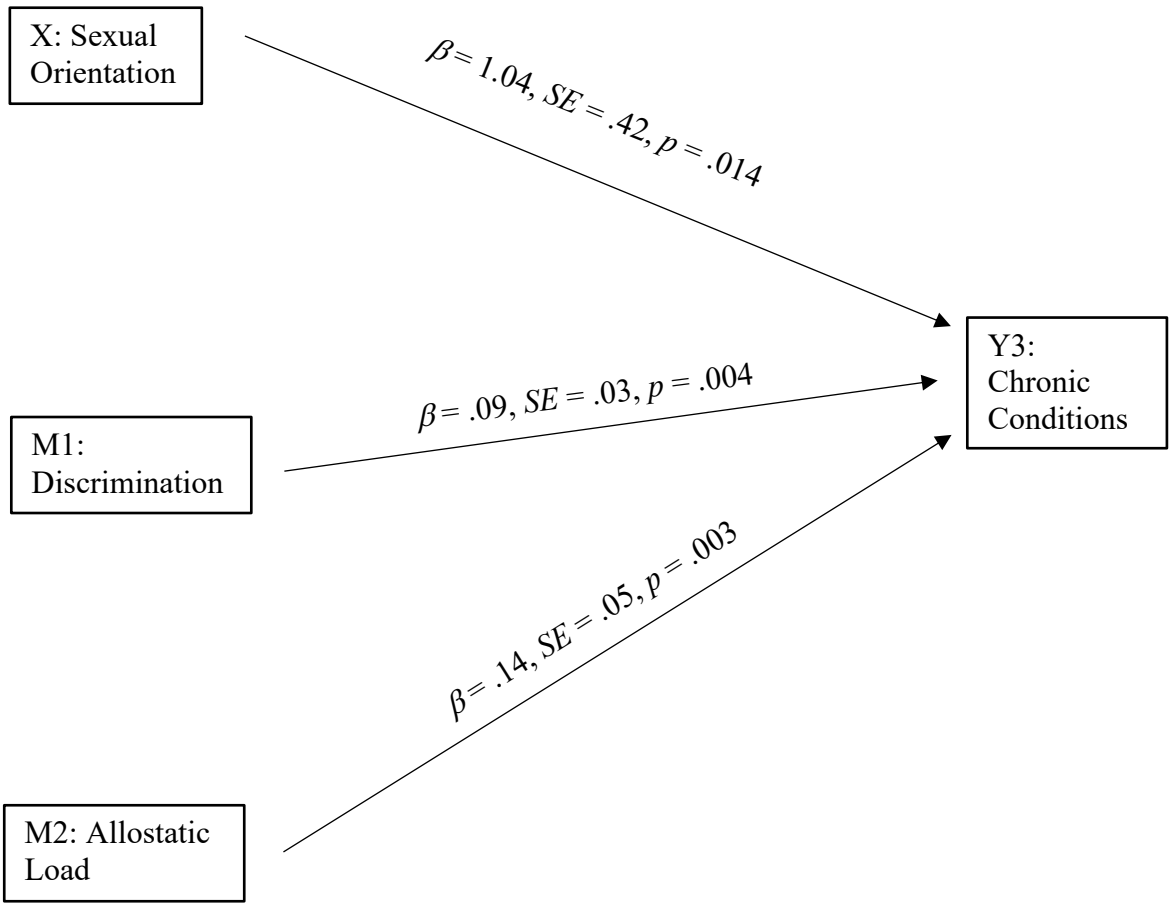

Figure 4. Path coefficients for the direct effects model.

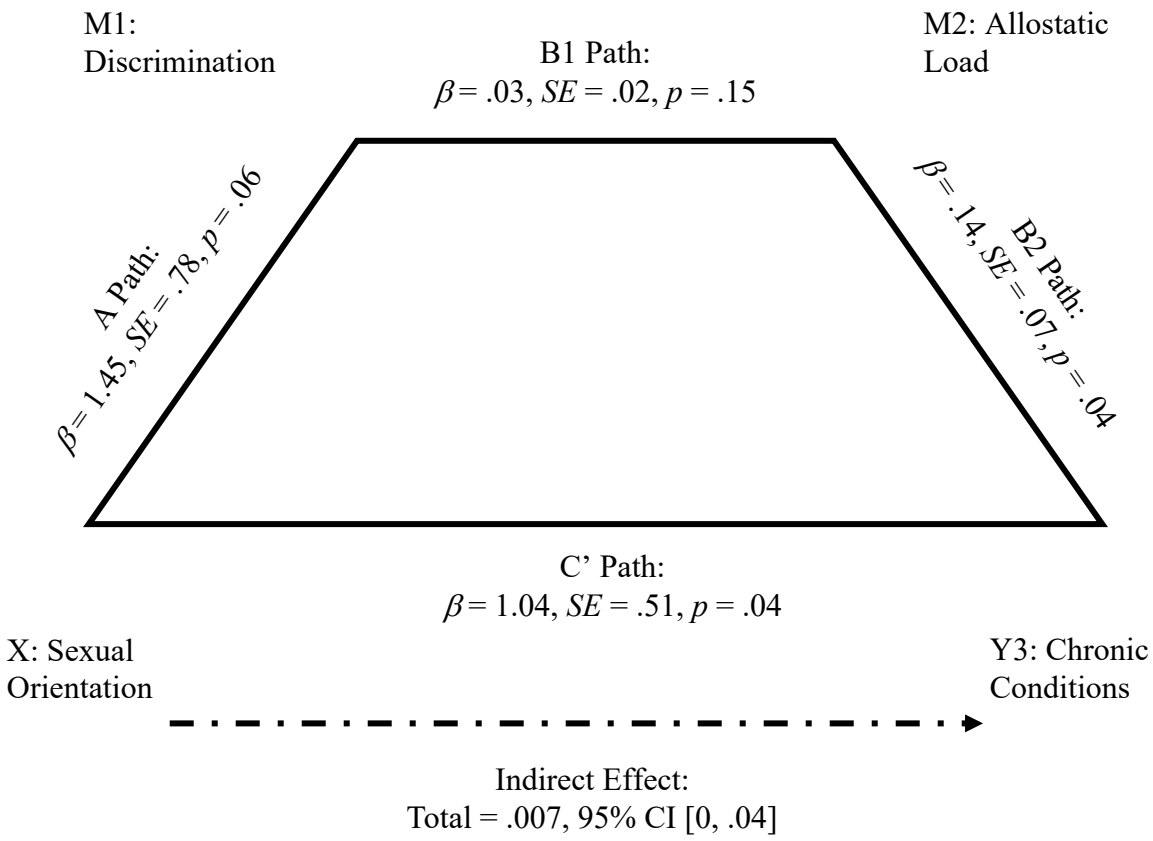

Figure 5. Path coefficients for the final mediation model.

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