UNIVERSITY OF CALIFORNIA,
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Biopsychosocial Indicators of Depression and Suicidality in Medical Students

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Public Health

by

Kathleen M. Carlos

Dissertation Committee:
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2020

DEDICATION

To

my grandparents, Clara and Ernie Carlos.

Thank you for your sacrifice, love, and support.

Rest easy, grandpa.

We did it.

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Thank you all for investing in me and my future.

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ABSTRACT OF THE DISSERTATION

Biopsychosocial Indicators of Depression and Suicidality in Medical Students

By

Kathleen Carlos

Doctor of Philosophy in Public Health

University of California, Irvine, 2020

Assistant Professor Kristina Uban, Co-Chair

Assistant Professor Jenna Riis, Co-Chair

Background: Physicians die by suicide at a rate that is higher than the general population. This increased risk for suicide may begin during medical school. Medical students experience depression and suicidal thoughts and behaviors at a higher rate than their age-matched peers. This dissertation examines biopsychosocial risk factors for depression and suicidality in a sample of medical students. This dissertation also explores the use of salivary biomarkers as screening tools for mental distress by examining associations between indicators of depression and suicidality, salivary cortisol, and salivary C-reactive protein (CRP). *Methods*: An in-person, self-report survey was completed by 134 medical students. The survey contained questions about sociodemographic characteristics, family history of depression and suicide, and validated measures of health behaviors and psychosocial well-being. Participants also completed two consecutive days of saliva collection at home. Saliva samples were returned by 109 (81%) of the

134 medical students enrolled in the study. Cortisol and CRP were assayed from whole saliva in duplicate. Chapter 2 characterizes the prevalence of indicators of mental distress and potential risk factors, and examines sex differences using chi-square and Mann Whitney U tests. Additionally, associations between indicators of mental distress and potential risk factors including perceived stress, sleep quality, impostor syndrome, alcohol abuse, and financial distress (e.g. difficulty paying bills, financial need, and food insecurity) are examined using logistic regression. Chapter 3 examines associations between daily cortisol activity (i.e. daily output and diurnal slope) and indicators of mental distress using a linear multilevel model to asses variation in cortisol activity across people, sampling days, and individual salivary assessments. Chapter 4 explores associations between mental distress indicators and: 1) inflammatory activity (i.e. waking and evening CRP and diurnal CRP slope) using logistic regression and 2) the coordination between hypothalamic-pituitary-adrenal axis (HPA) and inflammatory function (i.e., waking and evening cortisol/CRP, the interaction between area under the curve with respect to ground (AUCg) for cortisol and CRP, and the interaction between diurnal slopes for cortisol and CRP). Sex-specific differences in waking and evening cortisol/CRP between mental distress groups (i.e., positive versus negative DS) are examined using Mann-Whitney U test. The interaction of cortisol AUCg and CRP AUCg and the interaction between cortisol diurnal slope and CRP diurnal slope are explored through logistic regression. *Results*: I found a high prevalence of DS, SI, history of suicidality, and factors shown to increase risk for suicide (i.e., poor sleep quality, high perceived stress and impostor syndrome, and high alcohol use). Positive DS was associated with high perceived stress, poor sleep quality, impostor syndrome, and bill payment difficulty after adjustment for demographic covariates and family history of depression. SI and suicide risk were associated with impostor feelings even

after adjustment, and history of suicidality was associated with impostor feelings and poor sleep quality even after adjustment. I also found that suicide risk was associated with higher diurnal cortisol output. Additionally, I found that waking CRP was positively associated with SI in males and females and DS in males, and negatively associated with suicide risk in females. Higher waking cortisol/CRP was also associated with a positive DS and suicide risk in females. The interaction between cortisol and CRP activity (i.e., AUCg and diurnal slope) was not associated with mental distress. *Conclusion*: These findings suggest a high prevalence of factors that are associated with increased risk for suicide in this sample, and that sleep quality, perceived stress, feelings of impostor syndrome, and bill payment difficulty may be important targets for future intervention studies in medical students. Additionally, this dissertation provides preliminary evidence that HPA and inflammatory activity are disrupted in a sample of young adults with mental distress. Future longitudinal research is needed to assess temporality of these findings, confirm these associations in a larger study sample, and provide additional evidence to inform mental health intervention and prevention efforts in this high-risk population.

CHAPTER 1
Introduction

Suicide is a major public health issue that takes more than 48,000 American lives and an estimated 1,000,000 lives across the globe each year (Centers for Disease Control and Prevention & National Center for Injury Prevention and Control, 2019; World Health Organization, 2016). While suicide is the tenth leading cause of death in the United States (Centers for Disease Control and Prevention & National Center for Injury Prevention and Control, 2019), physicians die by suicide at a rate that is much higher than the general population. Male physicians die by suicide at a rate 40% higher than men in the general population, and female physicians die by suicide at a rate 130% higher than women in the general population (Lindeman et al., 1996; E. S. Schernhammer & Colditz, 2004). The literature often cites a study that reports that 379 physicians die by suicide each year (Frank et al., 2000). In reality, this 379 figure only represents the suicide deaths of white male physicians in 28 states in 1990. In other words, this study did not include suicide data from 22 states (including California, Texas, and Florida, the three most populous states), and did not include female or non-white male suicide death data. Thus, the number of physicians lost to suicide each year is likely much higher than 379 at present, especially since the suicide rate in the United States has increased between 1% and 2% each year since 1999 (Hedegaard H, Curtin SC, 2018). The high suicide rate in physicians is thought to arise from a variety of factors including stressful work-life imbalance and lack of social connectedness due to excessively long work hours, alcohol abuse, increased incidence of untreated depression potentially due in part to mental health stigma in the medical field, and

access to lethal means such as medication (Bright & Krahn, 2011; K. J. Gold et al., 2013; Mata et al., 2015; Schwenk et al., 2008).

Many of these mental health burdens are also experienced by medical students. Before beginning medical school, medical students are similar to the general population in terms of burnout rates, incidence of depression, and ratings of quality of life (Brazeau et al., 2014). However, this similarity does not last, as medical students exhibit higher rates of burnout, depression, and thoughts of suicide (suicidal ideation) relative to the age-matched population (see Table 1 for relevant definitions) (Dyrbye et al., 2008, 2014; Substance Abuse and Mental Health Services Administration, 2019). This shift in mental health suggests that factors related to the context or experience of medical training may increase risk for depression and suicidal thoughts and behaviors in trainees. Medical school is an incredibly stressful part of a physician's training. This research aims to advance our understanding of the biopsychosocial factors related to mental distress in medical students with the long-term goal of informing targeted intervention and prevention programs and policies for this high-risk population.

Table 1. Terms and Definitions

Atypical Depression	Atypical depression is a subtype of major depression that is characterized by mood reactivity (positive change in mood in response to positive news or events) in addition to at least two of the following symptoms: increased appetite and weight gain, hypersomnia, severe fatigue referred to as leaden paralysis which causes the individual to feel physically weighed down, and increased sensitivity to interpersonal rejection (American Psychological Association (APA), 2013).
Depression	Also referred to as major depression or clinical depression, depression refers to a period of at least two weeks in which five or more of the following symptoms are experienced in addition to depressed mood or loss of interest or pleasure in daily activities: significant (>5% in one month) unintentional weight loss/gain or decrease/increase in appetite, sleep disturbance (insomnia or hypersomnia), tiredness, fatigue, or loss of energy, slowing or agitation of thoughts and/or movement that is observable by others, feelings of worthlessness or excessive guilt, trouble

	with concentration and/or decision making, and recurring thoughts of death (American Psychological Association (APA), 2013).
Melancholic Depression	Melancholic depression is a subtype of major depression that is characterized by lack of mood reactivity to positive news or events, unintentional weight loss or decreased appetite, symptoms of major depression that are worse in the morning, lack of energy, insomnia, and intense feelings of worthlessness and/or despair (American Psychological Association (APA), 2013).
Suicidal Ideation	Suicidal ideation is a term used to describe thoughts of suicide (Crosby et al., 2011).
Suicide Plan	Thoughts about attempting suicide that include planning elements such as method, time, and place (SAMHSA, 2014).
Suicide Attempt	Suicide attempt occurs when an individual injures themselves with the intent of causing their own death, but does not die (Crosby et al., 2011).
Suicide	Suicide is a death that results from self-injury with the intent to die by the self-injury (Crosby et al., 2011).
Suicidality	The term suicidality encompasses all suicidal behaviors including suicidal ideation, suicide planning, suicide attempt, and suicide. More specific terminology (i.e. suicidal ideation) should be used when possible (Meyer et al., 2010).

Prevalence of Depression and Suicidal Ideation Among Training and Practicing Physicians

A nationwide study on medical student and physician mental health found that 58.2% of medical students screened positive for major depression based on the two-item Primary Care Evaluation of Mental Disorders (PRIME-MD), and 9.4% had thoughts of suicide within the previous 12 months (Dyrbye et al., 2014). A more recent meta-analysis reported a pooled crude prevalence of 27.2% for depression and 11.1% for suicidal ideation in medical students (Rotenstein et al., 2016). As previously mentioned, these rates are much higher than what is experienced by the general population. According to the National Survey on Drug Use and Health (NSDUH), between 8% and 13.8% of adults experienced at least one major depressive episode in 2018 (Substance Abuse and Mental Health Services Administration, 2019). Lastly, yearly estimates of suicidal ideation among adults in the general population range from 2.5% to

4.7% (Park-Lee et al., 2013; Substance Abuse and Mental Health Services Administration, 2019).

The elevated prevalence of suicidal ideation seen in medical students does not appear to be an effect of higher education in general. A large study of 11,314 non-medical graduate students found that 4% of students experienced thoughts of suicide in the previous year (Brownson et al., 2011). This does not seem to be the case for depression, however. In a study addressing graduate student mental health (N = 3,040), 27.2% felt depressed, 22.8% felt hopeless, and 2.8% had considered suicide in the previous year (Wyatt & Oswalt, 2013). Although these findings do not include a depression screen, we know from the DSM-5 criteria and from previous research that depressed mood and hopelessness are important diagnostic criteria for depression (Parker, 2014). Lastly, a more recent study surveying 2,279 graduate students from 26 different countries found a 39% prevalence of moderate to severe depression using the Patient Health Questionnaire-9 (PHQ-9) (Evans et al., 2018). What is it about medical training that is associated with suicide? The answer does not seem to be depression alone. The following sections explore salient risk factors for suicidal thoughts and behaviors.

Suicide Risk Factors

Suicide occurs as a result of a complex combination of psychological, biological, and sociological factors that are highly individual, which makes suicide prevention efforts challenging (R. C. O'Connor & Nock, 2014; Turecki & Brent, 2016). In the general population, the risk factors most consistently associated with suicide in the literature include psychiatric disorders, history of suicide attempt, lack of social connectedness, physical illness, substance use

disorders, problems at work, and early-life adversity (Franklin et al., 2017; Hawton et al., 2013; Van Orden et al., 2010; World Health Organization, 2012). Risk factors that are associated with suicidality in medical students include low quality of life, performing at the clinical levels of training (e.g., third and fourth years of medical school), being female, stigma associated with seeking help for mental distress, debt concerns, alcohol abuse, social isolation, and heavy workload (Brazeau et al., 2014; Dyrbye et al., 2008, 2006; Goebert et al., 2009; Jackson et al., 2016; Rotenstein et al., 2016; Schwenk et al., 2010).

There are several potential risk factors for suicidality that are relevant to medical students that have yet to be explored in this population. For example, sleep dysregulation (i.e. insomnia, poor sleep quality, and insufficient duration of sleep) is associated with depression (Alvaro et al., 2013; Luca et al., 2013; Tsuno et al., 2005), suicidal ideation, suicide risk, and suicide (Bernert et al., 2017, 2015; Malik et al., 2014; Russell et al., 2019). Compared to the general population, medical students do not have adequate sleep (Azad et al., 2015; Brick et al., 2010). Inadequate sleep has been associated with burnout, high stress, and low academic performance in medical students (Almojali et al., 2017; Pagnin et al., 2014; Wolf & Rosenstock, 2017). This dissertation explores the relationship between depression, suicidality, and sleep quality in medical students. This line of research hopes to shed light on the associations between mental distress and poor sleep quality in medical students as such findings could be used to support changes in medical school policies in curricular structure.

Another potential risk factor for suicidality in medical students is impostor syndrome. Impostor syndrome, first described by Clance and Imes, is characterized by the inability of a successful individual to internalize a sense of accomplishment or belonging, and instead

attributes their success to luck or error (Chrisman et al., 1995; Clance & Imes, 1978). Individuals with impostor syndrome doubt their skills and abilities, and are often fearful of being discovered as an impostor, or as someone who does not belong (Villwock et al., 2016). A recent review of impostor syndrome in medical students cites prevalence among studies between 20-60% (Gottlieb et al., 2020). Impostor syndrome is associated with burnout, psychological distress, perfectionism, female sex, and low self-esteem in medical students (Gottlieb et al., 2020; Henning et al., 1998; Villwock et al., 2016) and low-self esteem, depression, and anxiety in physicians (Gottlieb et al., 2020; Oriel et al., 2004). The association between impostor syndrome and suicidality has yet to be explored in this population: a gap in knowledge which this dissertation will address.

Another potential risk factor that has not been explored in the literature is the effect of current financial difficulties on medical student well-being. Economic hardship is associated with suicidal ideation in undergraduate students and the general population (Fiksenbaum et al., 2017). Financial difficulties are a considerable concern for medical students and physicians: the average debt incurred from medical school has risen from $32,000 in 1986 to $190,000 in 2016 (Grischkan et al., 2017). Medical school debt is associated with burnout and low quality of life in physicians (Phillips et al., 2016; West et al., 2011) but the association between current financial difficulties, depression, and suicidality has not been assessed in medical students. In this dissertation, the association between financial distress (i.e. difficulty paying bills, food insecurity, and financial need), depression, and suicidality is considered in medical students.

Salivary Biomarkers as an Objective Indicator of Physiological Risk

In addition to several unexplored psychosocial factors that may be contributing to mental distress in the medical trainee community, there have also been limited investigations into the biological correlates and mechanisms underlying depression and suicide risk in this population. The following section discusses the need for an objective indicator of physiological risk in the medical community.

While seeking professional help is always advisable in situations of depression and suicidality, the literature has shown over and over that medical students and physicians alike are not comfortable seeking help (Arnhart et al., 2019; Bartlett & Fowler, 2019; Center et al., 2003; K. J. Gold et al., 2016; Schwenk et al., 2010). This is due, largely in part, to the stigmatization of mental illness in the medical community and the concern that seeking help will jeopardize an individual's reputation, career prospects, and medical board licensure (Adams et al., 2010; Bartlett & Fowler, 2019; Chew-Graham et al., 2003; Givens & Tjia, 2002; J. A. Gold et al., 2015; K. J. Gold et al., 2016; Hassan et al., 2009; Kuhn & Flanagan, 2017; Moutier, 2018; Schwenk et al., 2008, 2010). This stigma may also prevent medical students and physicians from taking signs of mental distress within themselves seriously (Bartlett & Fowler, 2019; K. J. Gold et al., 2016). Given the potential stigma-induced barriers to obtaining support for mental health, it is important for this population to have a mechanism through which members can better understand the severity of their symptoms and their downstream effects.[1] Having access to a biological, objective measure of depression and suicide risk may assist this population in moving

[1] For more on policies for how mental health is handled among physicians, and how this promotes further stigma, see Chapter 5.

past stigma and addressing their need for medical help. For example, the brain disease model of addiction has not only shifted the perspective that addiction is the result of bad behavior, but has also elucidated new avenues of research that have led to increased treatment effectiveness and more informed public health policy (i.e. the Mental Health Parity and Addiction Equity Act of 2008) (Barnett et al., 2018; Volkow et al., 2016). With this long-term goal in mind, this dissertation examines the use of salivary biomarkers as potential early indicators of depression and suicide risk. For example, the use of biomarkers for early detection of disease has been demonstrated in Alzheimer's disease through the use of neuroimaging and cerebrospinal fluid (CSF) biomarkers (Jack, 2012), and in schizophrenia through the use of eye movement tests (Benson et al., 2012). Detecting risk early, perhaps before depression or suicidality is clinically evident, may improve clinical outcomes through early treatment efforts (Boksa, 2013).

Cortisol and C-reactive protein (CRP) as salivary biomarkers

This dissertation addresses gaps in our current understanding of biological risk for depression and suicide in medical students. This work also makes advances toward the overarching goal of biomarker development for mental distress in the medical community by assessing relations between mental distress and levels of two biomeasures: cortisol and C-reactive protein (CRP). These measures were chosen because they index functioning in two physiologic systems associated with depression and suicidality pathophysiology that can be modified through behavioral changes (i.e. stress management and sleep).

Cortisol is a glucocorticoid produced by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress and, independently of stress, cortisol follows a diurnal (i.e. daily) rhythm

(Adam et al., 2017). This diurnal rhythm is characterized by high waking levels that peak approximately 30 minutes after waking, followed by a decline throughout the day with an evening nadir (J. C. Pruessner et al., 1997). Cortisol is independently associated with depression and suicidality. Depressed individuals have increased daily cortisol output relative to non-depressed controls (Pariante & Lightman, 2008). There is also evidence of impaired negative feedback of cortisol within the HPA axis among those experiencing mental distress. For example, dexamethasone, a synthetic adrenal steroid and glucocorticoid receptor agonist, fails to induce cortisol suppression in individuals with major depression (Paslakis et al., 2011). Cortisol concentrations are also associated with lifetime history of suicidality. Those with a history of suicide attempt or suicide ideation had significantly lower cortisol awakening responses (CAR) and flatter wake-peak to 12 hour slopes compared to those with no history of suicidality (O'connor et al., 2020). Additionally, lower baseline plasma cortisol is associated with personal and family history of suicidal behaviors (McGirr et al., 2011), and salivary cortisol is lower in suicide attempters relative to those with thoughts of suicide, and those without a suicidal history (Melhem et al., 2016). A recent study examined temporality of HPA axis activity relative to suicide attempt or suicide ideation by analyzing cortisol in scalp hair. Cortisol concentrations were lower in the hair of first time suicide attempters relative to individuals with suicide ideation without attempt, and healthy controls (Melhem et al., 2017). What is unclear is the extent to which HPA dysregulation occurs in young individuals in the early stages of depression and suicidality, a gap that this dissertation aims to address.

C-reactive protein (CRP), an acute phase protein released by the liver in response to systemic inflammation (S. Black et al., 2004), is positively associated with depression

(Valkanova et al., 2013). In a study of depressed psychiatric inpatients, serum CRP levels were positively associated with a history of suicide attempt and the risk of suicide attempt increased as CRP levels increased in a dose-response fashion. Additionally, patients with a history of suicide attempt were twice as likely to have high levels of CRP compared to patients without history of suicide attempt (Courtet et al., 2015). Higher serum CRP concentrations have also been observed in suicide attempters relative to those who have suicidal ideation but have not attempted suicide (Melhem et al., 2017). There is also evidence of differences in inflammation among individuals with high and low suicidal ideation. Depressed inpatients with high suicidal ideation had a higher inflammatory index (composite variable encompassing plasma concentrations of TNF-α, IL-6, IL-10, CRP) than depressed inpatients with low suicidal ideation (O'Donovan et al., 2013). We do not know the extent to which CRP is associated with depression and indices of suicidality in early stages of these disorders. What is also not explored in the literature is the association of CRP with depression and suicidality at different times across the day, and the change of CRP across the day (i.e. diurnal slope). CRP peaks upon waking and decreases throughout the day (Izawa et al., 2013), similar to the diurnal pattern of cortisol (i.e. morning high and decrease throughout the day) (Kirschbaum & Hellhammer, 1994) which may indicate the need to explore diurnal CRP activity the way in which diurnal cortisol activity is examined (i.e. area under the curve and diurnal slope).

Consideration of both cortisol and CRP together may be more predictive of depression and suicide risk than assessments of either measure in isolation. There is a bi-directional feedback loop between the HPA axis and the immune system. In response to a stressor, the hypothalamus releases corticotropin-releasing hormone (CRH), which signals the anterior

pituitary to release adrenocorticotropin (ACTH), which in turn stimulates the adrenal glands to secrete cortisol (Silverman et al., 2003; Silverman & Sternberg, 2012). Proinflammatory cytokines (e.g. TNF-α, IL-1, IL-6) stimulate each level of the HPA axis, and in a homeostatic system, cortisol acts to suppress immune activity and each level of the HPA axis (Silverman et al., 2003). Dysregulation of this feedback loop between the HPA axis and immune system is associated with depression (Pariante & Lightman, 2008). And more recently, the literature has highlighted an association between this dysregulation and suicide attempt in clinical populations (Courtet et al., 2016). What is less well known is whether this neuroendocrine-immune (NEI) dysfunction is present in the early stages of depression and suicidality.

One study in a healthy community sample of individuals without a history of depression found that higher depressive symptoms was associated with a low ratio of cortisol/CRP in women, suggesting early involvement of NEI dysfunction (Suarez et al., 2015) in depressive symptomatology. This dissertation builds on the work that considers the bidirectional feedback loop between the HPA axis and immune system and its association with depression through application to a high-risk population: medical students. Beyond application to a sample of physician trainees, these series of analyses begin to address an important gap in the literature in considering bidirectional feedback between HPA and immune function in association with indices of suicidality. Additionally, the involvement of cortisol and CRP as measures of depression and suicide risk in a non-clinical sample of young adults is not well-explored in the literature, and it is a gap that this dissertation aims to address.

Guiding Models of Suicide Risk and Conceptual Framework for this Research

A meta-analysis conducted on the last 50 years of longitudinal suicide research found that thus far, our ability to predict suicidal behaviors based on risk factors is no better than chance (Franklin et al., 2017). The authors suggest that this is a result of risk factors being studied in isolation, and that the combined effect of multiple risk factors has not been adequately considered. To facilitate understanding of the effect of multiple risk and protective factors on risk for suicide, a guiding and actionable conceptual framework is needed. The following section will discuss the Interpersonal Theory of Suicide (IPT) and the Integrated Motivational-Volitional (IMV) model of suicidal behavior, and how I suggest applying them to better understand suicide risk in medical students.

In the past decade, much work has been done on the development of theoretical models to better understand suicide risk. Perhaps the most widely known is Joiner's Interpersonal Theory (IPT) of Suicide. The two main interpersonal constructs of the proposed theory are thwarted belongingness and perceived burdensomeness (Van Orden et al., 2010). There is a basic human need to belong (Baumeister & Leary, 1995), and when this need is thwarted, an individual is likely to experience loneliness and perhaps even social isolation, which is an empirically demonstrated risk factor for suicide (Turecki & Brent, 2016; Van Orden et al., 2010). Joiner suggests that when thwarted belongingness and perceived burdensomeness are coupled with the acquired capability to engage in suicidal behavior, it will lead to lethal or near-lethal suicide attempts (Van Orden et al., 2010). We can think about "acquired capability" as the combination of certain factors that predispose one to suicide, including the loss of fear about dying, and an increased ability to deal with pain (Van Orden et al., 2010). According to the IPT, in addition to

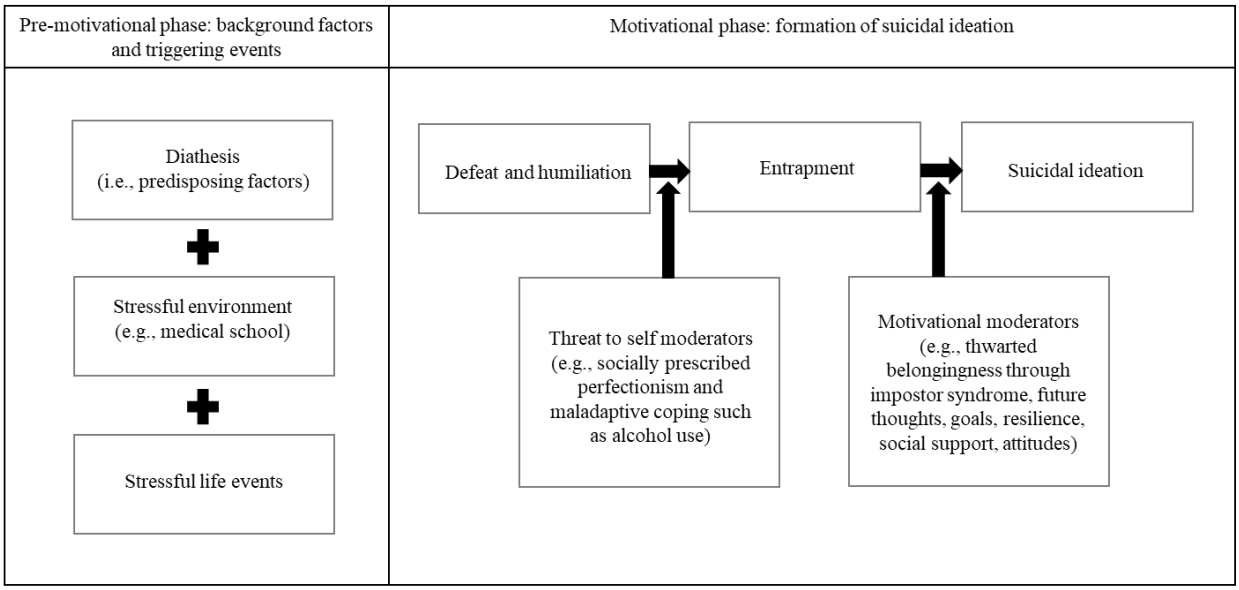
their importance in the acquired capability for suicide, predisposing factors "increase risk for suicide [only] through their relationship with both thwarted belongingness and perceived burdensomeness." For example, Joiner suggests that both childhood adversity and psychological disorders may create the perception of not belonging or of being a burden, which would lead to increased capacity for psychological and physical pain, which ultimately increases both the risk and the capability for suicide. Although this reasoning is logical, I think that this is an oversimplification of the role that predisposing factors play in suicide risk. For example, chronic stress experienced during childhood (i.e., due to low socioeconomic status or abuse) has been associated with increased inflammation in adulthood, which is thought to mediate the association between childhood stress and the empirically demonstrated increased risk for cardiovascular disease, diabetes, cancer, depression, and suicide (Fagundes et al., 2013; Fagundes & Way, 2014; Miller et al., 2011). Additionally, adults who were abused as children have been shown to rate more daily events as stressful, and may have heightened emotional reactivity to stress compared to adults who were not abused as children (Glaser et al., 2006). Increased inflammation, stressful life-events, and heightened emotional reactivity are all associated with suicide risk (Hawton & van Heeringen, 2009; R. C. O'Connor & Kirtley, 2018). Suicide risk is determined by a complex interaction of biopsychosocial factors that are more complicated than an increased capacity for pain.

A model that builds on the IPT that I expect to be more relevant to medical students is the integrated motivational-volitional (IMV) model of suicidal behavior. The IMV model is a biopsychosocial framework that describes how defeat and entrapment drives suicidal ideation (R. C. O'Connor & Kirtley, 2018). There are three phases of the IMV model: the pre-motivational

phase includes background factors and triggering events, the motivational phase includes the formation of suicidal ideation and suicidal intention, and the volitional phase includes the enaction of suicidal behavior (suicide planning and attempt). The pre-motivational phase acknowledges the role that biological, genetic, and cognitive vulnerability factors play in the development of suicide risk. According to O'Connor and Kirtley, these factors include childhood adversity, cortisol dysregulation, decreased serotonergic transmission, and negative life events. The IMV model has origins in the diathesis-stress model (Schotte & Clum, 1987), which suggests that suicidal ideation develops when personal vulnerability factors are coupled with stressful life events and/or a stressful environment. During the motivational phase, "[the authors] posit that appraisals of defeat and/or humiliation from which there is no perceived escape—a sense of entrapment—are the proximal predictors of suicidal ideation" (R. C. O'Connor & Kirtley, 2018). This concept of entrapment is the bridge between feelings of defeat and development of suicidal ideation. It is during the motivational phase that protective and risk factors (i.e., motivational moderators) determine whether an individual transitions from feelings of entrapment to thoughts of suicide. Protective motivational moderators include social connectedness, belongingness, positive thoughts about the future, goal pursuit, and reasons for living (R. C. O'Connor et al., 2009; R. C. O'Connor & Kirtley, 2018; R. C. O'Connor et al., 2015; Van Orden et al., 2010; You et al., 2011). Deleterious motivational moderators include burdensomeness, little to no social connectedness, and lack of resilience (Q. Chang et al., 2017; J. Johnson et al., 2010; Van Orden et al., 2010). If an individual enters the volitional phase, the transition from suicidal ideation to action (i.e. suicide attempt) only occurs in the presence of volitional moderators, which can be psychological, physiological, social, or environmental in

origin. Examples of volitional moderators include access to lethal means (environmental), past suicidal behavior (psychological), exposure to the suicidal behavior of others (social), impulsivity, increased sensitivity to physical pain (physiological), and fearlessness about death (Hawton & van Heeringen, 2009; R. C. O'Connor & Kirtley, 2018; Van Orden et al., 2010).

Figure 1. Modified Integrated Pre-Motivational and Motivational Model of Suicidal Behavior



This is modified version of the IMV Model of Suicidal Behavior adapted from (O'Connor & Kirtley, 2018).

To understand the pathway toward developing increased suicide risk in medical students, this dissertation research focuses on the pre-motivational (i.e. predisposing risk factors) and motivational (i.e. formation of suicidal ideation) phases of the IMV model, with the addition of the IPT's thwarted belongingness construct in terms of impostor syndrome. Because this study is concerned with understanding risk factors for suicidal ideation and overall suicide risk, and not the transition to suicide attempt, the volitional phase was not appropriate for the current investigation. The design of this dissertation research was informed by a conceptual framework

that drew from the IMV and IPT models with modifications introduced to adapt these frameworks to the specific needs and risks of the medical trainee community. This dissertation does not address all aspects of the modified Integrated Pre-motivational and Motivational Model of Suicidal Behavior (Figure 1), but instead focuses on the most modifiable aspects of the model. Modifications and additions to the model are described below.

In the pre-motivational phase of the model, predisposing factors were changed to include those thought to be especially salient among medical students, namely depression, poor sleep quality, inflammation, and NEI dysfunction, among the salient predisposing factors listed above. The medical school environment, which is stressful in general, is highlighted in this framework and an important factor contributing to mental distress. In addition, predisposing factors may influence the extent to which students consider medical training stressful. For example, poor sleep quality and depression independently increase individual susceptibility to stress (Liu & Alloy, 2010; Prather et al., 2013). The final set of factors in the pre-motivational phase of the model, stressful life events, is expanded to include financial distress, as economic hardship is associated with sensitivity to stress and to pain (Rios & Zautra, 2011). In the motivational phase of the model, defeat and humiliation are adapted in this framework to include poor academic performance in medical school, which can be lead to low feelings of self-worth and to avoidant coping mechanisms (e.g. alcohol use) (Dahlin et al., 2011). Relevant threat to self moderators in medical students include alcohol misuse and socially prescribed perfectionism, which is defined as the high expectations that we believe others have for us (Smith et al., 2018). Alcohol misuse is associated with maladaptive coping in medical students, and is also associated with increased risk for suicide in physicians (Dahlin et al., 2011; Dyrbye et al., 2006; Martinez et al., 2016).

Socially prescribed perfectionism is associated with low psychological quality of life, burnout, and impostor syndrome in medical students and physicians (Henning et al., 1998; Robertson & Long, 2019; Smith et al., 2018). A salient motivational moderator in this population is thwarted belongingness, which can be conceptualized as impostor syndrome in medical students. The chronic feelings of inadequacy and incompetency that accompanies impostor syndrome (Robertson & Long, 2019) are likely to influence feelings of thwarted belongingness and therefore increase the risk of developing suicidal ideation. Lastly, motivational moderators that are protective against the development of suicidal ideation include positive thoughts about the future, resilience, and social support (R. C. O'Connor & Kirtley, 2018; Van Orden et al., 2010).

Research Aims

Guided by this conceptual framework and the overarching goal of supporting mental well-being in the medical professional community, the following chapters address key gaps in our understanding of depression and suicide risk during medical training. Within a sample of medical students, this research addresses the following specific aims:

(1) Examine and characterize the prevalence of mental distress (e.g., positive depression screen, suicidal ideation in the previous 12 months, suicide risk, and history of suicidality), and potential risk factors for mental distress (e.g. perceived stress, sleep quality, impostor syndrome, bill payment difficulty, food insecurity, financial need, and alcohol use).

(2) Examine behavioral and psychological risk factors for mental distress.

(3) Evaluate associations between mental distress HPA axis activity, including a) diurnal cortisol output; and b) diurnal cortisol slope.

(4) Explore associations between mental distress and measures of NEI functioning, including a) morning and evening CRP concentrations; b) diurnal CRP slope; and c) coordination of the HPA axis and inflammatory activity.

CHAPTER 2
Behavioral and Psychosocial Correlates of Mental Distress Among Medical Students

Physicians die by suicide at a rate that is between 40% (male physicians) and 130% (female physicians) higher than the general population (E. Schernhammer, 2005; E. S. Schernhammer & Colditz, 2004). The suicide rate of the general population in the United States has been increasing by between 1% and 2% each year since 1999 (Hedegaard, Curtin, & Warner, 2018), and I expect the rate of physician suicide has increased as well. Physicians also experience depression at a rate that is higher than the general population (Center et al., 2003). Depression is an established precipitating risk-factor for suicide. An estimated 50-66% of suicide decedents have a depressive disorder at the time of death (Hawton et al., 2013; Turecki & Brent, 2016). However, only 2-6% of people with major depressive disorder die by suicide (Bostwick & Pankratz, 2000; Van Orden et al., 2010), suggesting that depression, in isolation, does not cause suicide. Rather, depression increases the risk of dying by suicide when in conjunction with other biopsychosocial factors (Van Orden et al., 2010). For physicians, other biopsychosocial factors that may contribute to suicide include stressful work, stigma against mental illness, loneliness, substance abuse, and access to lethal means such as medication (Schernhammer, 2005; Dyrbye et al., 2006).

It is currently unknown when increased suicide risk in physicians begins, and here I assess depression and suicide risk during medical school and hypothesize that this may be the point at which increased risk emerges. Before beginning medical school, medical students have similar rates of burnout and depression, and similar levels of self-reported quality of life ratings

when compared to the general population (Brazeau et al., 2014), but this trend does not last. Medical students have a higher prevalence of depression and thoughts of suicide (suicidal ideation) than both the age-matched population and graduate students in other disciplines (Dyrbye et al., 2008, 2014; Park-Lee et al., 2013; Substance Abuse and Mental Health Services Administration, 2019). A large nationwide study found that 58.2% of medical students screened positive for depression and 9.4% endorsed suicidal ideation (SI) within the previous 12 months (Dyrbye et al., 2014). These rates are much higher than rates of major depression and SI reported by the general population (7.7-13.1%, and 4.3-10.5%, respectively ((Park-Lee et al., 2013; Substance Abuse and Mental Health Services Administration, 2018).

This shift in mental health suggests that something about medical training is increasing the risk for depression and suicidal thoughts and behaviors among trainees. More research efforts are needed to increase our understanding of risk factors for depression and suicide (e.g. SI, suicide risk, suicidal thoughts and behaviors) among medical students. Through increased understanding, intervention and prevention programs could help prevent the increased risk among medical providers, possibly during medical school training.

Modifiable Risk Factors

This study addresses this gap in knowledge by examining the factors associated with depression and suicide risk among medical students. Relations between positive depression screen (DS), SI, suicide risk, and history of suicidality (i.e. suicidal thoughts and behaviors) were examined alongside select modifiable psychosocial and behavioral risk factors including sleep quality (Grady & Roberts, 2017; K. M. Johnson et al., 2017; Wolf & Rosenstock, 2017), stress

(Heinen et al., 2017; Ziegelstein, 2018), alcohol use (Ayala et al., 2017; Jackson et al., 2016), feelings of impostor syndrome (Gottlieb et al., 2020; Hutchins & Rainbolt, 2017), and financial distress (Eisenberg et al., 2007; Fiksenbaum et al., 2017). These risk factors represent potential targets for future prevention and intervention efforts that support mental and emotional wellness among this unique, high risk population of future healers.

Here, among a sample of medical students, two research questions are addressed.

1) What are the prevalences of mental distress indicators (depression, SI, suicide risk, and history of suicidality) and mental distress risk factors (poor sleep quality, perceived stress, alcohol use, feelings of impostor syndrome, and financial distress) among medical students? Do prevalences differ between males and females?

I hypothesize that this sample will have higher depressive symptoms and SI than typically reported by studies of the general population. Rates of overall suicide risk and history of suicidality are not well-explored in medical students nor in the general population, but I expect the prevalence to be high given the previously demonstrated high rate of SI among medical students in prior studies (Dyrbye et al., 2014). I also expect high levels of self-reported poor sleep quality, perceived stress, alcohol use, and feelings of impostor syndrome. I do not expect high levels of financial distress in this population because 73-79% of the students entering medical school over the past 30 years have been from the top two quintiles of household income (Youngclaus & Roskovensky, 2018). Based on this finding, I expect that approximately one-fifth of medical students will be experiencing financial distress.

Because there are sex differences in physician suicide relative to suicide in the general population, possibly suggesting the need for more support for female physicians, I characterized the sample by sex. We expect female students to report higher depression, suicidality, and feelings of impostor syndrome relative to male students. This hypothesis is based on evidence of a culture in medicine that is discriminatory against women (Bruce et al., 2015; Jagsi et al., 2016; Witte et al., 2006), which may contribute to higher mental distress in female students. I expect similar rates of perceived stress, sleep quality, alcohol use, and financial distress between male and female students.

2) Which risk factors are associated with 2a) a positive depression screen (DS), 2b) SI in the previous year, 2c) suicide risk, and 2d) suicidal history? Additionally, I assess whether relations between the risk factors and mental distress indices remain after controlling for important individual characteristics, including sex, year in medical school, race, ethnicity, and family history of depression and suicide. Finally, I examine the independent contributions of suicidality risk factors by assessing relations between these factors and suicidal risk after controlling for levels of depressive symptoms.

I hypothesize that poor sleep quality, high perceived stress, high feelings of impostor syndrome, high alcohol use, and financial distress will be associated with a positive depression screen, SI, and suicide risk. I also expect to see these indicators of distress in those with a history of suicidality.

Methods

Study design and participants

All students enrolled in a large, southern California medical school in 2018-19 were eligible to participate in this cross-sectional study. The only exclusionary criterion was the inability to read English, but this did not exclude anyone in this sample. Participants were recruited through in-person and email announcements. Participants completed a pen and paper, in-person survey containing questions about sociodemographic characteristics, family history of depression and suicide, and validated measures of health behaviors and psychosocial well-being. Study participation was voluntary, and all survey responses were anonymized. Participants were compensated $25 for their time. Study and recruitment procedures and materials were approved by the University's Institutional Review Board prior to recruitment.

Measures

Depressive Symptoms and Depression Screen

Responses on the Patient Health Questionnaire-9 (PHQ-9) were used to assess depressive symptom severity in the past two weeks. The PHQ-9 focuses on the nine DSM-IV diagnostic criteria for depressive orders (Kroenke & Spitzer, 2002). The PHQ-9 has good reliability (Cronbach's alpha values range from 0.86-0.89) and has been validated for use in student and general population samples (Kroenke et al., 2001). PHQ-9 scores range from 0-27 with scores of 5, 10, 15, and 20 corresponding to mild, moderate, moderately severe, and severe depressive symptoms, respectively (Kroenke et al., 2010). A cut-off score of 10 has been consistently

recommended as a threshold for identifying individuals experiencing major depressive disorder with 88% sensitivity and 88% specificity (Kroenke et al., 2010; Manea et al., 2015). Here I refer to this cut-off as a positive depression screen (DS). I dichotomized PHQ-9 scores using the recommended threshold to examine risk factors associated with a positive DS (PHQ9 score ≥10). Depressive symptoms are presented in Table 2 in their categorical form for characterization purposes (research question 1).

Suicidality

Responses on the Suicidal Behaviors Questionnaire-Revised (SBQ-R) were used to assess three unique indicators of suicidality: SI in the previous 12 months, lifetime history of suicidality, and overall suicide risk based on global scores. The SBQ-R is validated for use in college students and in the general population with good reliability (Cronbach's alpha values ranging from 0.76-0.87). Scores range from 3-18 with a cut-off score of 7 having optimal sensitivity (93%) and specificity (95%) to differentiate between non-suicidal and suicidal individuals (Osman et al., 2001). All three indicators of suicidality were used as dichotomous variables created using established cut-offs (Osman et al., 2001).

Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) was used to assess participant perceived sleep quality over the past 30 days. PSQI scores range from 0-21 with higher scores indicative of worse sleep. The PSQI has been validated in clinical and nonclinical populations (Grandner et al., 2006) with a mean Cronbach's alpha value of 0.83 and adequate test-retest reliability. A

score ≥5 differentiates poor sleep quality with 89.6% sensitivity and 86.5% specificity (Buysse et al., 1988). Here, a dichotomous variable was created using the suggested cut-off for characterization of the sample (Table 2) while the continuous PSQI score was used in logistic regression analyses.

Alcohol Use

Participant responses on the Alcohol Use Disorders Identification Test-C (AUDIT-C) were used to assess hazardous drinking and/or active alcohol use disorders (Bush et al., 1998). AUDIT-C scores range from 0-12, with scores ≥4 indicative of a positive screen for men, and scores ≥3 a positive screen for women. It has been validated in both men and women and has adequate sensitivity and specificity for identifying hazardous drinking and/or active alcohol use disorder. The recommended cut-off scores have 86% sensitivity and 72% specificity for identifying hazardous drinking and/or active alcohol use disorders in men, and 66% sensitivity and 94% specificity likewise in women (Bush et al., 1998). AUDIT-c scores were dichotomized separately for males and females using validated cut-off scores for the presence or absence of hazardous drinking.

Perceived Stress

Responses on the Perceived Stress Scale-10 (PSS-10) were used to measure the extent to which an individual considers their life to be stressful in the past 30 days (Cohen, 1988). Scores range from 0 to 40, with higher scores indicating higher perceived stress. Scores <13 indicate low perceived stress, 14-26 indicate moderate perceived stress, and ≥27 indicate high perceived

stress (Lee, 2012). The PSS-10 has been validated in the general population, adults, college and graduate students, and in clinical populations (Lee, 2012). It has adequate internal reliability, with Cronbach's alpha coefficients ranging between 0.74 and 0.91, and test-retest reliability greater than 0.70 (Lee, 2012). Here, a categorical variable was created using the suggested cut-offs for the characterization of the sample while continuous PSS scores were used in logistic analyses.

Financial Distress

Questions about financial distress were adapted from the Center for Disease Control and Prevention's Behavioral Risk Factor Surveillance System Questionnaire (Centers for Disease Control, 2013) and included three questions: "In general, would you say you have more money than you need, just enough for your needs, or not enough to meet your needs?", "How difficult is it to pay your monthly bills – very difficult, somewhat, not very, or not at all difficult?", and "In the past 12 months did you not have enough money to buy food – often, sometimes, rarely, or never?" Due to small cell sizes, these variables were dichotomized for analyses: financial need was coded as "yes" if participant selected the "not enough" category, bill payment difficulty was coded as "yes" if participant selected "very" or "somewhat", and food insecurity was coded as "yes" if participant selected "often" or "sometimes". Participants that selected "prefer not to answer" were considered missing in analyses (n=3).

Impostor Syndrome

Responses on the Clance Imposter Syndrome (CIS) scale were used to assess the extent to which participants feel their accomplishments are due to luck or chance instead of ability and the perceived feeling of impostorism (Clance & Imes, 1978). Cronbach's alpha values range between 0.84 and 0.96 and the CIS has been validated for use in clinical and general population samples including student populations (Holmes et al., 1993). Scores range between 20 and 100 with scores <40 classified as few impostor characteristics (IC), 41-60 as moderate IC, 61-80 as frequent IC, and >80 as intense IC (Chrisman et al., 1995; Holmes et al., 1993).
Here, a categorical variable was created using the suggested cut-offs for characterization of the sample and continuous CIS scores were used in analyses.

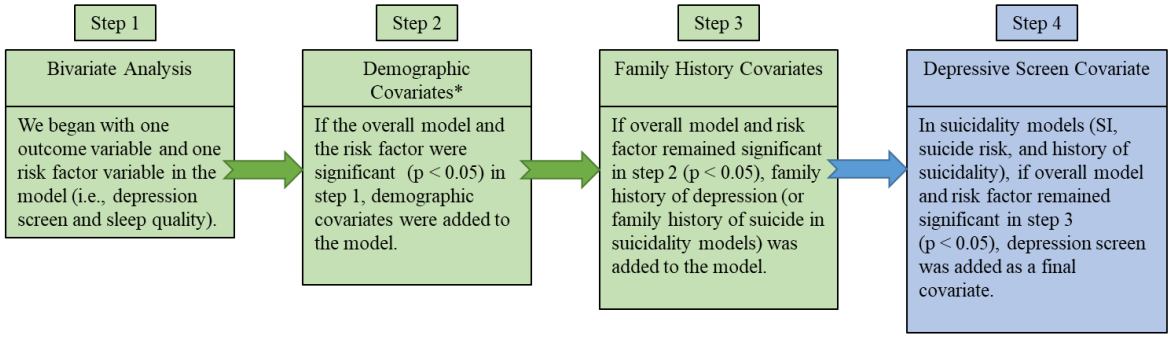
Covariates

It is important to account for demographic characteristics and family history of depression (Monroe et al., 2014) and suicide (Hawton et al., 2013) when examining associations between risk factors and mental distress indicators. I included sex (Pospos et al., 2019; Riecher-Rössler, 2017), year in medical school (Schwenk et al., 2010), race, and ethnicity (Cheref et al., 2015) as covariates in step 2 of analyses (Figure 1). In step 3, I controlled for family history of disease (depression or suicide depending on the model). Questions about family history were adapted from the Center for Disease Control and Prevention's Behavioral Risk Factor Surveillance System Questionnaire (Centers for Disease Control, 2013).

Statistical Analysis

To address the first research question, I used descriptive statistics to characterize the sample, and chi squared tests compared mental distress indicators and mental distress risk factors across sex. To address each component of the second research question, I conducted a series of logistic regression models (See Figure 1 for a flow chart). Separate models were created to assess relations between each dichotomous mental distress indicator (DS, SI in the previous 12 months, history of suicidality, and overall suicide risk score) and each risk factor. Research question 2 was not analyzed separately by sex due to sample size concerns. If models remained significant through step 3, predicted probabilities were computed and plotted for each model to visualize the marginal effects across mental distress groups (i.e. positive versus negative DS) (Williams, 2012). Model robustness was verified through postestimation analyses examining multicollinearity of independent variables, goodness of fit, and area under ROC curve. Postestimation analysis also included sensitivity analyses based on residuals, leverage, and influence diagnostics to ensure that individual observations were not driving the models. Statistical analyses were performed using Stata/SE 15.1.

Figure 1. Logistic Regression Flow Chart



The purpose of step 1 was to determine if the outcome variable (DS, SI, suicide risk, history of suicidality) was significantly associated with each risk factor (sleep quality, alcohol use, stress, impostor-feelings, difficulty paying bills, financial need, and food insecurity).
*The purpose of step 2 was to control for demographic characteristics including sex, race, ethnicity, age, and year in medical school.
The purpose of step 3 was to determine if the association between mental distress outcome and risk factor held significance even after controlling for family history of disease.
The purpose of step 4 was to determine if the risk factor was associated with the suicidality outcome, independently of depression screen.

Results

Table 1. Sample Demographics

		n (%)
Year in Medical School	First (MS1)	42 (31.34)
	Second (MS2)	24 (17.91)
	Third (MS3)	31 (23.13)
	Fourth (MS4)	37 (27.61)
Sex	Male	64 (47.76)
	Female	70 (52.24)
Age	22-24	49 (36.57)
	25-27	57 (42.54)
	28-30	24 (17.91)
	31-33	3 (2.23)
	34-37	1 (0.75)

Race	Asian	62 (45.93)
	White	59 (43.70)
	Other/Prefer not to answer	14 (10.37)
Hispanic/Latino Origin	Yes	23 (17.16)
	No	108 (80.60)

Table 2. Sample Characteristics - Mental Distress Indicators and Risk Factors

		Total	**Males**	**Females**
		n (%)		
Depression screen (DS)	Positive	22 (16.42)	8 (12.50)	14 (20.0)
	Negative	112 (83.58)	56 (87.5)	56 (80.0)
Depressive symptom severity	Minimal or none	79 (58.96)	40 (62.50)	39 (55.71)
	Mild	33 (24.63)	16 (25)	17 (24.29)
	Moderate to moderately severe	22 (16.42)	8 (12.50)	14 (20)
Family history of depression diagnosis	Yes	49 (36.57)	22 (34.38)	27 (38.57)
	No	66 (49.25)	34 (53.13)	32 (45.71)
	Do not know	19 (14.18)	8 (12.5)	11 (15.71)
SI in the previous 12 months	Yes	23 (17.16)	14 (21.88)	9 (12.86)
	No	111 (82.84)	50 (78.13)	61 (87.14)
History of suicidality	Yes	46 (34.33)	23 (35.94)	23 (32.86)
	No	88 (65.33)	41 (64.06)	47 (67.14)

Suicide risk screen	Positive	14 (10.45)	8 (12.50)	6 (8.57)
	Negative	120 (89.55)	56 (87.50)	64 (91.43)
Family history of suicide	Yes	17 (12.69)	7 (10.94)	10 (14.29)
	No	116 (86.57)	57 (89.06)	59 (84.29)
Hazardous drinking screen	Positive	67 (50)	23 (35.94)	44 (62.86)
	Negative	67 (50)	41 (64.06)	26 (37.14)
Sleep quality	Good	55 (41.04)	28 (43.75)	27 (38.57)
	Poor	79 (58.96)	36 (56.25)	43 (61.43)
Perceived stress	Low	60 (44.78)	39 (60.94)	21 (30.0)
	Moderate	68 (50.75)	21 (32.81)	47 (67.14)
	High	6 (4.48)	4 (6.25)	2 (2.86)
Impostor feelings	Few	7 (5.22)	4 (6.25)	3 (4.29)
	Moderate	63 (47.01)	35 (54.69)	28 (40.0)
	Frequent	45 (33.58)	16 (25.0)	29 (41.43)
	Intense	19 (14.18)	9 (14.06)	10 (14.29)
Bill payment difficulty	Yes	33 (25.00)	14 (22.22)	19 (27.54)
	No	99 (75.00)	49 (77.78)	50 (72.46)
Financial need	Yes	23 (17.29)	10 (15.62)	13 (18.84)
	No	110 (82.71)	54 (84.37)	56 (81.15)
Food insecurity	Yes	19 (14.18)	11 (17.19)	8 (11.43)
	No	115 (85.82)	53 (82.81)	62 (88.57)

Sample Characterization (Research Question 1)

134 medical students completed the study, with 0% attrition rate. Table 1 outlines the demographics of the sample.

Mental Distress Indicators

Sample characteristics by sex can be found in Table 2. Approximately 41% of participants reported at least mild depressive symptoms, and 16% screened positive for depression. There were no significant differences in depressive symptoms by sex ($p = 0.242$). Approximately 17% endorsed SI in the previous 12 months, 10% had a positive suicide risk score, and more than one-third of participants reported a history of suicidality. There were no significant differences in SI ($p = 0.167$), suicide risk ($p = 0.548$), or history of suicidality by sex ($p = 0.708$). The majority of those with SI in the previous 12 months (74% (17/23)) did not have a positive DS.

Risk Factors

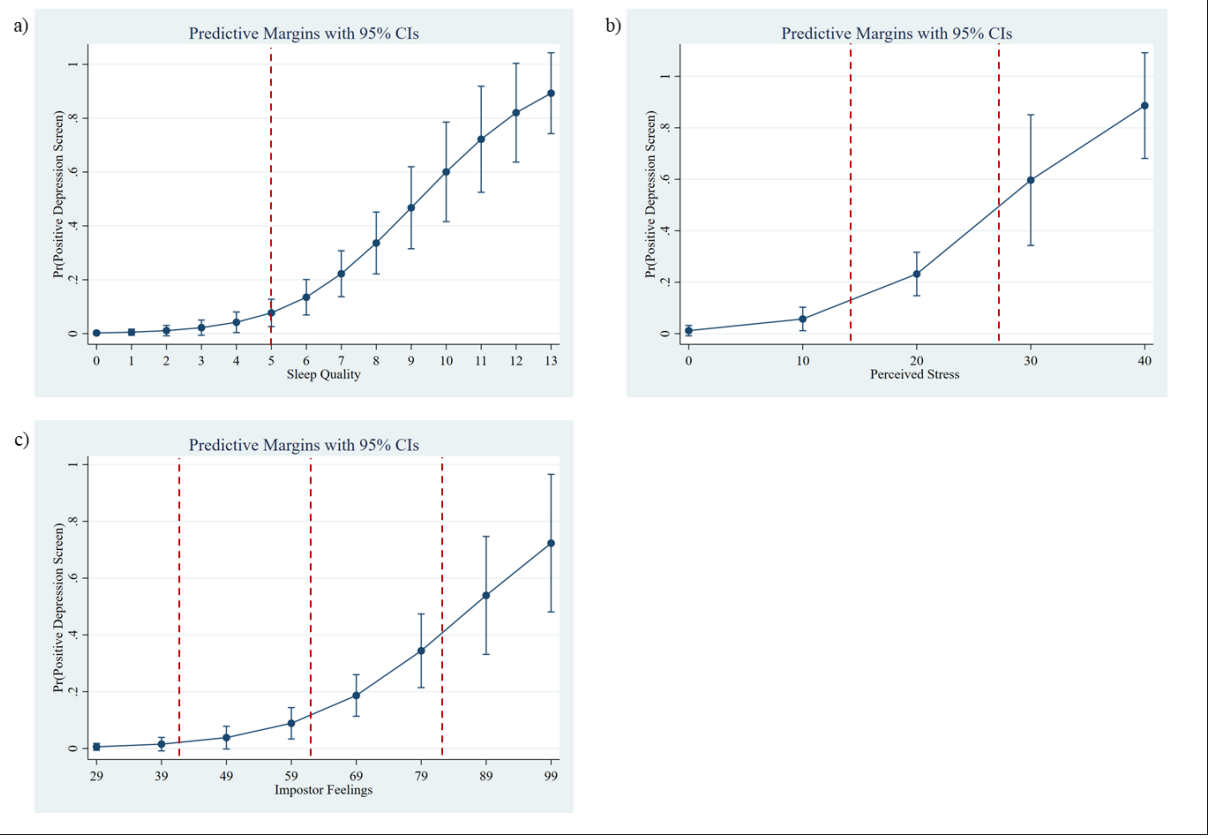
Half of the sample (67/134) screened positive for hazardous drinking, and females were more likely than males to have a positive screen ($p = 0.002$). Fifty-eight percent (79/134) of participants had poor quality sleep, 55% (74/134) had at least moderate perceived stress, 47% (64/134) had frequent or intense impostor feelings, and between 14% and 25% of participants reported current financial distress (see Table 2). There were no additional significant differences by sex.

Risk Factors Associated with a Positive DS (Research Question 2a)

DS was associated with sleep quality even after adjustment for all covariates (OR: 2.25, $p < 0.001$, 95% CI: 1.56 – 3.25). Among scores indicative of poor sleep quality (≥ 5) the predicted probability of having a positive DS increased from 7.6% at a score of 5 (95% CI: 0.026 – 0.127,

p < 0.05), to 89.2% (95% CI: 0.743 – 1.04, p < 0.001) at a sleep quality score of 13 (the maximum reported in the sample) (Figure 2a; panel a).

Figure 2a. Predicted Probabilities of Positive DS by Sleep Quality, Stress, and Impostor Feelings



Probability of positive DS was predicted after logistic regression for each risk factor model that remained significant after adjustment for covariates. Predicted probabilities are from fully adjusted (up to step 3 in Figure 1) models. Dashed lines refer to cut-offs indicating a) poor sleep quality, b) moderate stress (14-26) and high stress (≥27), and c) moderate impostor feelings (41-60), frequent impostor feelings (61-80), and intense impostor feelings (≥81).

DS was also associated with perceived stress even after adjustment for all covariates (OR: 1.22, p < 0.001,95% CI: 1.09 – 1.35) (Table 3a). The predicted probability of having a positive DS increased from 18.7% (95% CI: 0.063 – 0.310, p < 0.01), to 95.9% (95% CI: 0.849 – 1.07, p < 0.001) as perceived stress scores increased from moderate to high (Figure 2a; panel b).

DS was also associated with impostor feelings even after adjustment for all covariates (OR: 1.10, $p < 0.001$, 95% CI: 1.06 – 1.16) (Table 3a). As impostor feelings increased from moderate to intense, the predicted probability of having a positive DS increased from 8.87% ($p < 0.01$, 95% CI: 0.033 – 0.144) to 72.32% ($p < 0.001$, 95% CI: 0.481 – 0.966) (Figure 2a; panel c).

The odds of having a positive DS was 3.43 times higher for an individual who has difficulty paying bills relative to an individual who does not ($p < 0.05$, 95% CI: 1.02 – 11.5) (Table 3a). The predicted probability of having a positive DS increased from 11.7% ($p < .001$, 95% CI: 0.052 - 0.183) for those who have no difficulty paying bills, to 28.2% ($p < 0.01$, 95% CI: 0.120 – 0.443) for those who do have difficulty paying bills.

Financial need, food insecurity, and hazardous alcohol use were not associated with DS.

Table 3a. Relationship Between Positive Depression Screen and Risk Factors									
Risk factors and covariates	**Step 1 - Bivariate analysis**			**Step 2 - Demographic covariates**			**Step 3 - Family history of depression**		
	OR	**p**	**95% CI**	**OR**	**p**	**95% CI**	**OR**	**p**	**95% CI**
Sleep quality	1.96	0.000	1.49 - 2.57	2.21	0.000	1.55 - 3.15	2.25	0.000	1.56 - 3.25
Female	-	-	-	4.33	0.062	0.92 - 20.24	4.59	0.055	0.967 - 21.81
Race									
White	-	-	-	0.47	0.350	0.102 - 2.23	0.49	0.373	0.103 - 2.33
Other	-	-	-	0.09	0.087	0.006 - 1.41	0.10	0.101	0.006 - 1.56
Hispanic/Latino	-	-	-	3.80	0.168	0.564 - 26.87	3.53	0.205	0.502 - 24.92
Year									
MS2	-	-	-	0.76	0.777	0.109 - 5.21	0.77	0.800	0.108 - 5.55
MS3	-	-	-	0.18	0.124	0.022 - 1.57	0.19	0.127	0.021 - 1.60
MS4	-	-	-	0.02	0.010	0.001 - 0.40	0.02	0.010	0.001 - 0.393
Age	-	-	-	1.39	0.104	0.93 - 2.07	1.40	0.094	0.94 - 2.10
Family history[a]	-	-	-	-	-	-	0.69	0.637	0.15 - 3.18
Stress	1.2	0.000	1.10 - 1.31	1.22	0.000	1.09 - 1.36	1.22	0.000	1.09 - 1.35
Female	-	-	-	2.06	0.259	0.585 - 7.29	1.95	0.305	0.543 - 7.01
Race									
White	-	-	-	0.45	0.258	0.114 - 1.788	0.42	0.226	0.100 - 1.72
Other	-	-	-	0.12	0.105	0.0096 - 1.54	0.10	0.092	0.007 - 1.45
Hispanic/Latino	-	-	-	4.98	0.052	0.989 - 25.08	5.50	0.047	1.02 - 29.56
Year									
MS2	-	-	-	0.81	0.779	0.177 - 3.64	0.78	0.745	0.168 - 3.57
MS3	-	-	-	0.31	0.153	0.0602 - 1.55	0.31	0.155	0.0603 - 1.56
MS4	-	-	-	0.10	0.039	0.011 - 0.892	0.11	0.044	0.012 - 0.942

Age	-	-	-		1.37	0.036	1.020 - 1.859		1.35	0.049	1.001 - 1.843
Family history[a]					-	-	-		1.46	0.55	0.415 - 6.497
Impostor feelings	1.08	0.000	1.04 - 1.13		1.10	0.000	1.05 - 1.16		1.10	0.000	1.05 - 1.16
Female	-	-	-		1.52	0.504	0.440 - 5.28		1.49	0.53	0.426 - 5.22
Race											
White	-	-	-		1.26	0.758	0.284 - 5.62		1.21	0.8	0.265 - 5.54
Other	-	-	-		0.39	0.428	0.037 - 4.01		0.37	0.41	0.033 - 3.96
Hispanic/Latino	-	-	-		5.49	0.037	1.10 - 27.28		5.7	0.04	1.11 - 29.2
Year											
MS2	-	-	-		0.94	0.938	0.185 - 4.73		0.92	0.92	0.182 - 4.662
MS3	-	-	-		0.24	0.117	0.040 - 1.428		0.24	0.12	0.038 - 1.440
MS4	-	-	-		0.09	0.031	0.010 - 0.799		0.09	0.03	0.842 - 1.57
Age	-	-	-		1.15	0.351	0.851 - 1.57		1.15	0.38	0.842 - 1.57
Family history[a]	-	-	-		-	-	-		1.21	0.76	0.338 - 4.36
Bill Difficulty											
Yes	4.45	0.003	1.67 - 11.80		3.17	0.05	0.989 - 10.32		3.43	0.05	1.02 - 11.5
Female	-	-	-		1.38	0.56	0.460 - 4.19		1.39	0.56	0.454 - 4.25
Race											
White	-	-	-		0.55	0.36	0.460 - 4.19		0.55	0.36	0.152 - 1.97
Other	-	-	-		0.2	0.17	0.156 - 1.95		0.18	0.16	0.016 - 1.95
Hispanic/Latino	-	-	-		3.52	0.17	0.019 - 1.98		3.61	0.1	0.786 - 16.6
Year											
MS2	-	-	-		0.71	0.57	0.158 - 3.20		0.63	0.56	0.131 - 3.00
MS3	-	-	-		0.41	0.26	0.083 - 1.96		0.41	0.27	0.082 - 2.00
MS4	-	-	-		0.11	0.03	0.014 - 0.796		0.1	0.03	0.012 - 0.745

Age	-	-	-		1.12	0.18	0.914 - 1.48		1.21	0.22	0.895 - 1.634
Family history[a]	-	-	-		-	-	-		1.39	0.57	0.451 - 4.26
Financial need											
Yes	3	< 0.05	1.04 - 8.57		-	-	-		-	-	-
Food insecurity											
Yes	3.88	< 0.05	1.32 - 11.43		-	-	-		-	-	-
Alcohol abuse											
Yes	1	1	0.40 - 2.49		-	-	-		-	-	-
[a] Family history refers to family history of depression.											

Table 3b. Relationship Between Suicidal Ideation and Risk Factors															
Risk factors and covariates	**Step 1 - Bivariate analysis**				**Step 2 - Demographic covariates**				**Step 3 - Family history of depression**				**Step 4 - DS**		
	OR	**p**	**95% CI**		**OR**	**p**	**95% CI**		**OR**	**p**	**95% CI**		**OR**	**p**	**95% CI**
Sleep quality	1.24	0.015	1.04 - 1.47		1.25	0.04	1.01 - 1.55		1.25	0.04	1.01 - 1.54		1.23	0.09	0.96 - 1.57
Female	-	-	-		0.35	0.067	0.12 - 1.07		0.35	0.067	0.11 - 1.07		0.34	0.067	0.11 - 1.07
Race															
White	-	-	-		0.49	0.291	0.14 - 1.81		0.49	0.291	0.14 - 1.81		0.49	0.289	0.13 - 1.81
Other	-	-	-		1.24	0.823	0.18 - 8.49		1.24	0.823	0.18 - 8.47		1.27	0.807	0.18 - 8.74
Hispanic/Latino	-	-	-		2.52	0.254	0.51 - 12.42		2.52	0.257	0.51 - 12.45		2.50	0.262	0.50 - 12.46
Year															
MS2	-	-	-		0.09	0.045	0.01 - 0.95		0.09	0.045	0.01 - 0.95		0.08	0.045	0.01 - 0.95
MS3	-	-	-		0.74	0.680	0.19 - 2.96		0.74	0.678	0.19 - 2.96		0.76	0.692	0.18 - 3.02
MS4	-	-	-		0.31	0.177	0.05 - 1.70		0.31	0.179	0.05 - 1.72		0.31	0.201	0.05 - 1.84
Age	-	-	-		1.00	0.986	0.75 - 1.34		1.00	0.981	0.75 - 1.34		0.99	0.999	0.74 - 1.34
Family history[a]	-	-	-		-	-	-		1.03	0.964	0.24 - 4.47		1.04	0.957	0.24 - 4.50
DS	-	-	-		-	-	-		-	-	-		1.16	0.841	0.26 - 5.19
Stress	1.06	< .10	0.99 - 1.14		-	-	-		-	-	-		-	-	-
Impostor feelings	1.04	0.015	1.01 - 1.07		1.05	0.01	1.01 - 1.09		1.05	0.01	1.01 - 1.09		1.05	0.01	1.01 - 1.09
Female	-	-	-		0.25	0.027	0.07 - 0.85		0.25	0.025	0.07 - 0.84		0.25	0.025	0.07 - 0.84
Race															
White	-	-	-		0.67	0.561	0.17 - 2.59		0.65	0.537	0.16 - 2.56		0.64	0.523	0.16 - 2.54
Other	-	-	-		1.58	0.640	0.23 - 10.81		1.52	0.640	0.23 - 10.81		1.52	0.668	0.22 - 10.54
Hispanic/Latino	-	-	-		4.06	0.077	0.85 - 19.19		4.06	0.077	0.85 - 19.19		3.95	0.087	0.82 - 19.16
Year															

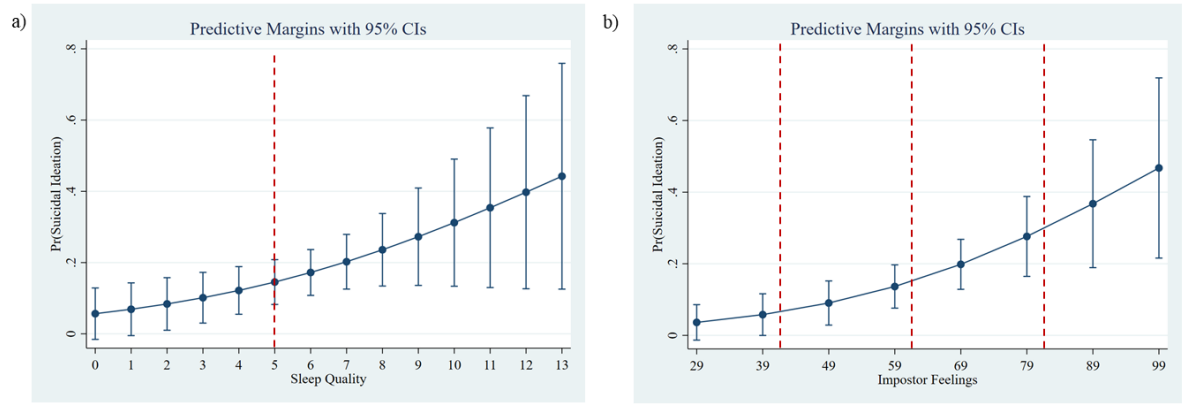
MS2	-	-	-		0.09	0.046	0.01 - 0.96		0.09	0.046	0.01 - 0.96		0.09	0.046	0.01 - 0.95
MS3	-	-	-		0.66	0.565	0.16 - 2.70		0.66	0.565	0.16 - 2.70		0.66	0.565	0.16 - 2.74
MS4	-	-	-		0.29	0.174	0.05 - 1.71		0.29	0.174	0.05 - 1.71		0.29	0.189	0.05 - 1.82
Age	-	-	-		0.93	0.677	0.69 - 1.27		0.93	0.677	0.69 - 1.27		0.93	0.686	0.69 - 1.27
Family history[a]	-	-	-		-	-	-		1.35	0.69	0.30 - 6.03		1.36	0.69	0.30 - 6.04
DS									-	-	-		1.18	0.82	0.29 - 4.78
Bill Difficulty															
Yes	1.39	> 0.10	0.51 - 3.76		-	-	-		-	-	-		-	-	-
Financial need															
Yes	0.67	> 0.10	0.18 - 2.49		-	-	-		-	-	-		-	-	-
Food insecurity															
Yes	1.34	> 0.10	0.40 - 4.50		-	-	-		-	-	-		-	-	-
Alcohol abuse															
Yes	0.58	> 0.10	0.23 - 1.46		-	-	-		-	-	-		-	-	-
[a] Family history refers to family history of suicide.															

Risk Factors Associated with SI (Research Question 2b)

Sleep quality was associated with SI after adjusting for all covariates (Table 3b). However, sensitivity analyses revealed that one participant was likely driving the association between SI and sleep quality. When dropped from the sleep quality model, the significance of the sleep quality covariate changed from p = 0.018 to p = 0.069. This participant had a high risk profile with a positive DS, SI in the previous 12 months, and the highest (poorest) sleep quality score in this sample.

Impostor feelings was also associated with SI even after adjustment for all covariates (OR: 1.05, p < 0.05, 95% CI: 1.01 – 1.09). This association remained significant even after controlling for DS (OR: 1.05, p < 0.05, 95% CI: 1.01 – 1.09). As impostor feelings score increased from moderate to intense, the predicted probability of having SI increased from 9.30% (p < 0.01, 95% CI: 0.031 – 0.155) to 43.3% (p < 0.01, 95% CI: 0.117 – 0.689) (Figure 2b; panel b).

Figure 2b. Predicted Probabilities of SI by Sleep Quality and Impostor Feelings



Probability of SI was predicted after logistic regression for each risk factor model that remained significant after adjustment for covariates. Predicted probabilities are from fully adjusted (up to step 3 in Figure 1) models. Dashed lines refer to cut-offs indicating a) poor sleep quality, and b) moderate impostor feelings (41-60), frequent impostor feelings (61-80), and intense impostor feelings (≥81).

Table 3c. Relationship Between Suicide Risk and Risk Factors														
Risk factors and covariates	**Step 1 - Bivariate analysis**				**Step 2 - Demographic covariates**				**Step 3 - Family history of depression**				**Step 4 - DS**	
	OR	**p**	**95% CI**		**OR**	**p**	**95% CI**		**OR**	**p**	**95% CI**		**OR**	**p**	**95% CI**
Sleep quality	1.24	0.039	1.01 - 1.52		1.22	0.111	0.95 - 1.56		-	-	-		-	-	-
Female	-	-	-		0.47	0.285	0.12 - 1.87		-	-	-		-	-	-
Race														
White	-	-	-		0.55	0.479	0.11 - 2.83		-	-	-		-	-	-
Other	-	-	-		4.42	0.173	0.52 - 37.51		-	-	-		-	-	-
Hispanic/ Latino	-	-	-		1.37	0.740	0.21 - 8.78		-	-	-		-	-	-
Year														
MS2	-	-	-		1.30	0.805	0.16 - 10.58		-	-	-		-	-	-
MS3	-	-	-		2.63	0.278	0.45 - 15.13		-	-	-		-	-	-
MS4	-	-	-		0.64	0.709	0.06 - 6.65		-	-	-		-	-	-
Age	-	-	-		1.04	0.804	0.74 - 1.45		-	-	-		-	-	-
Family history[a]	-	-	-		-	-	-		-	-	-		-	-	-
Stress	1.1	0.031	1.01 - 1.20		1.09	0.058	0.99 - 1.21		-	-	-		-	-	-
Female	-	-	-		0.39	0.195	0.09 - 1.60		-	-	-		-	-	-
Race														
White	-	-	-		0.50	0.413	0.09 - 2.59		-	-	-		-	-	-
Other	-	-	-		4.64	0.181	0.49 - 44.01		-	-	-		-	-	-
Hispanic/ Latino	-	-	-		1.50	0.671	0.23 - 9.81		-	-	-		-	-	-
Year														
MS2	-	-	-		1.41	0.745	0.17 - 11.36		-	-	-		-	-	-

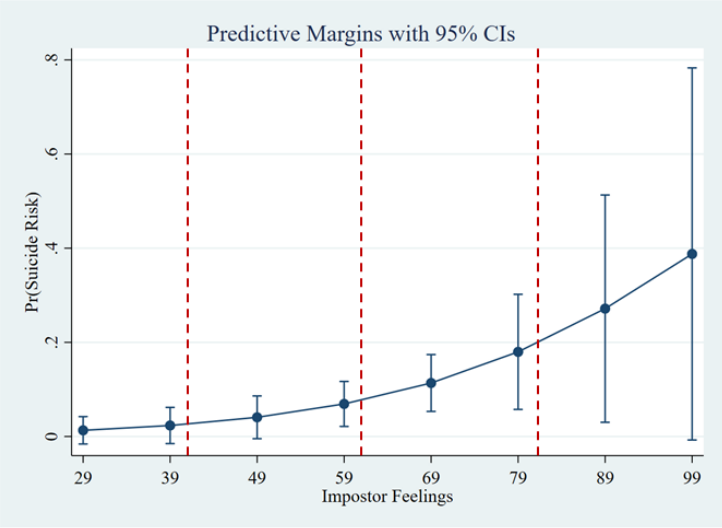
MS3	-	-	-		2.67	0.266	0.47 - 15.06		-	-	-		-	-	-
MS4	-	-	-		0.81	0.861	0.07 - 8.83		-	-	-		-	-	-
Age	-	-	-		1.04	0.796	0.74 - 1.48		-	-	-		-	-	-
Family history[a]	-	-	-		-	-	-		-	-	-		-	-	-
Impostor feelings	1.05	0.016	1.01 - 1.09		1.06	0.014	1.01 - 1.11		1.06	0.015	1.01 - 1.12		1.07	0.009	1.02 - 1.13
Female	-	-	-		0.44	0.265	0.10 - 1.87		0.41	0.247	0.09 - 1.83		0.41	0.246	0.09 - 1.85
Race															
White	-	-	-		0.76	0.763	0.13 - 4.53		0.58	0.575	0.09 - 3.79		0.61	0.601	0.09 - 3.94
Other	-	-	-		5.66	0.126	0.61 - 52.29		4.64	0.207	0.42 - 50.46		4.26	0.234	0.39 - 46.55
Hispanic/ Latino	-	-	-		2.14	0.409	0.35 - 13.13		2.37	0.376	0.35 - 16.06		3.23	0.251	0.44 - 24.06
Year															
MS2	-	-	-		1.50	0.711	0.17 - 13.07		1.32	0.805	0.14 - 12.27		1.54	0.711	0.16 - 14.97
MS3	-	-	-		2.68	0.280	0.45 - 16.01		2.60	0.311	0.41 - 16.68		2.49	0.337	0.39 - 16.03
MS4	-	-	-		0.67	0.754	0.06 - 7.78		0.67	0.762	0.05 - 8.72		0.53	0.647	0.04 - 7.76
Age	-	-	-		0.96	0.806	0.66 - 1.36		0.91	0.639	0.62 - 1.32		0.92	0.687	0.62 - 1.36
Family history[a]	-	-	-		-	-	-		3.16	0.130	0.71 - 14.08		3.39	0.115	0.74 - 15.46
DS									-	-	-		0.38	0.336	0.05 - 2.71
Bill Difficulty															
Yes	1.78	0.332	0.55 - 5.76		-	-	-		-	-	-		-	-	-
Financial need															
Yes	0.77	0.754	0.16 - 3.73		-	-	-		-	-	-		-	-	-

Food insecurity															
Yes	1.77	0.416	0.44 - 7.05		-	-	-		-	-	-		-	-	-
Alcohol abuse															
Yes	1	1	0.33 - 3.02		-	-	-		-	-	-		-	-	-
[a] Family history refers to family history of suicide.															

Risk Factors Associated with Suicide Risk (Research Question 2c)

Suicide risk was associated with impostor feelings even after adjustment for all covariates (OR: 1.06, $p < 0.05$, 95% CI: 1.01 – 1.12) and after controlling for DS (OR: 1.06, $p < 0.05$, 95% CI: 1.01 – 1.12) (Table 3c). As impostor feelings score increased from moderate to intense, the predicted probability of having a positive suicide risk score increased from 11.1% ($p < 0.001$, 95% CI: 0.055 – 0.165) to 35.2% ($p < 0.05$, 95% CI: 0.067 – 0.637) (Figure 2c). Suicide risk was also associated with sleep quality ($p < 0.05$) and perceived stress ($p < 0.05$) in bivariate analysis, but not after adjustment for covariates. Hazardous drinking screen, bill payment difficulty, financial need, and food insecurity were not associated with suicide risk.

Figure 2c. Predicted Probabilities of Suicide Risk by Impostor Feelings



Probability of having a positive suicide risk score was predicted after logistic regression for each risk factor model that remained significant after adjustment for covariates. Predicted probabilities are from fully adjusted (up to step 3 in Figure 1) models.
Dashed lines refer to cut-offs indicating moderate impostor feelings (41-60), frequent impostor feelings (61-80), and intense impostor feelings (≥81).

Risk Factors Associated with History of Suicidality (Research Question 2d)

History of suicidality was associated with impostor feelings after adjustment for all covariates (OR: 1.04 $p < 0.01$, 95% CI: 1.02 – 1.08), and after controlling for depression (OR: 1.04 $p < 0.05$, 95% CI: 1.01 – 1.08) (Table 3d). History of suicidality was also associated with sleep quality after adjustment for covariates (OR: 1.18, $p < 0.05$, 95% CI: 1.01 – 1.39), but not after controlling for depression. The predicted probability of having a suicidal history increased as sleep quality worsened (higher score), and as impostor feelings increased (Figure 2d). Perceived stress was associated with history of suicidality, but not after adjustment for covariates ($p = 0.052$).

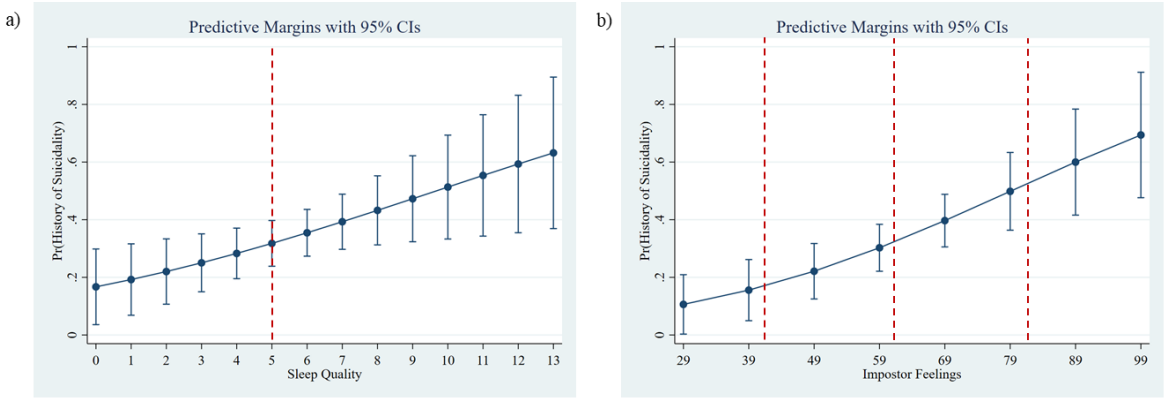
Hazardous drinking, bill payment difficulty, financial need, and food insecurity were not associated with history of suicidality.

Table 3d. Relationship Between Suicidal History and Risk Factors													
Risk factors and covariates	**Step 1 - Bivariate analysis**			**Step 2 - Demographic covariates**			**Step 3 - Family history of depression**			**Step 4 - DS**		
	OR	**p**	**95% CI**	**OR**	**p**	**95% CI**	**OR**	**p**	**95% CI**	**OR**	**p**	**95% CI**
Sleep quality	1.18	0.021	1.02 - 1.37	1.18	0.042	1.01 - 1.39	1.18	0.042	1.01 - 1.39	1.26	0.02	1.03 - 1.53
Female	-	-	-	0.63	0.267	0.27 - 1.43	0.63	0.281	0.27 - 1.45	0.66	0.346	0.28 - 1.54
Race												
White	-	-	-	0.27	0.007	0.10 - 1.39	0.27	0.007	0.10 - 0.70	0.26	0.006	0.09 - 0.67
Other	-	-	-	1.19	0.825	0.25 - 5.79	1.19	0.823	0.25 - 5.84	1.02	0.975	0.20 - 5.21
Hispanic/Latino	-	-	-	1.04	0.946	0.28 - 3.81	1.05	0.935	0.28 - 3.85	1.13	0.853	0.31 - 4.16
Year												
MS2	-	-	-	0.87	0.831	0.25 - 3.02	0.87	0.829	0.25 - 3.01	0.84	0.788	0.24 - 2.91
MS3	-	-	-	0.96	0.953	0.31 - 3.01	0.97	0.971	0.31 - 3.07	0.89	0.845	0.28 - 2.85
MS4	-	-	-	0.23	0.037	0.06 - 0.92	0.23	0.040	0.06 - 0.94	0.19	0.024	0.04 - 0.81
Age	-	-	-	1.09	0.441	0.87 - 1.36	1.09	0.443	0.87 - 1.36	1.12	0.321	0.89 - 1.41
Family history[a]	-	-	-	-	-	-	0.84	0.779	0.25 - 2.84	0.84	0.777	0.24 - 2.86
DS	-	-	-	-	-	-	-	-	-	0.46	0.239	0.13 - 1.67
Stress	1.07	0.025	1.01 - 1.13	1.06	0.052	0.99 - 1.13	-	-	-	-	-	-
Female	-	-	-	0.53	0.135	0.23 - 1.22	-	-	-	-	-	-
Race												
White	-	-	-	0.26	0.006	0.09 - 0.68	-	-	-	-	-	-
Other	-	-	-	1.26	0.772	0.26 - 6.15	-	-	-	-	-	-
Hispanic/Latino	-	-	-	1.18	0.791	0.33 - 4.22	-	-	-	-	-	-
Year												
MS2	-	-	-	0.81	0.736	0.24 - 2.77	-	-	-	-	-	-
MS3	-	-	-	0.91	0.872	0.29 - 2.83	-	-	-	-	-	-

MS4	-	-	-	0.25	0.049	0.06 - 0.99	-	-	-	-	-	-
Age	-	-	-	1.10	0.408	0.87 - 1.37	-	-	-	-	-	-
Family history[a]	-	-	-	-	-	-	-	-	-	-	-	-
Impostor feelings	1.05	0.001	1.02 - 1.08	1.05	0.003	1.02 - 1.08	1.05	0.003	1.02 - 1.08	1.05	0.001	1.02 - 1.09
Female	-	-	-	0.51	0.131	0.22 - 1.22	0.51	0.131	0.22 - 1.22	0.52	0.139	0.21 - 1.24
Race												
White	-	-	-	0.35	0.038	0.23 - 0.94	0.35	0.038	0.23 - 0.94	0.35	0.038	0.13 - 0.94
Other	-	-	-	1.55	0.595	0.31 - 7.78	1.55	0.595	0.31 - 7.78	1.42	0.675	0.27 - 7.42
Hispanic/Latino	-	-	-	1.35	0.643	0.38 - 4.77	1.35	0.643	0.38 - 4.77	1.58	0.483	0.44 - 5.74
Year												
MS2	-	-	-	0.95	0.944	0.27 - 3.37	0.95	0.944	0.27 - 3.37	0.94	0.929	0.27 - 3.32
MS3	-	-	-	1.01	0.985	0.32 - 3.24	1.01	0.985	0.32 - 3.24	0.92	0.890	0.28 - 3.01
MS4	-	-	-	0.26	0.061	0.06 - 1.06	0.26	0.061	0.06 - 1.06	0.21	0.038	0.05 - 0.92
Age	-	-	-	1.01	0.923	0.80 - 1.27	1.01	0.923	0.80 - 1.27	1.03	0.796	0.81 - 1.31
Family history[a]	-	-	-	-	-	-	0.98	0.982	0.28 - 3.37	0.98	0.985	0.28 - 3.44
DS							-	-	-	0.47	0.223	0.14 - 1.57
Bill Difficulty												
Yes	0.63	0.294	0.26 - 1.49	-	-	-	-	-	-	-	-	-
Financial need												
Yes	0.47	0.161	0.16 - 1.35	-	-	-	-	-	-	-	-	-
Food insecurity												
Yes	1.14	0.803	0.41 - 3.11	-	-	-	-	-	-	-	-	-

Alcohol abuse														
Yes	0.51	0.071	0.25 - 1.06		-	-	-		-	-	-		-	-	-
[a] Family history refers to family history of suicide.														

Figure 2d. Predicted Probabilities of Suicidal History by Sleep Quality and Impostor Feelings



Probability of having a history of suicidality was predicted after logistic regression for each risk factor model that remained significant after adjustment for covariates. Predicted probabilities are from fully adjusted (up to step 3 in Figure 1) models.
Dashed lines refer to cut-offs indicating a) poor sleep quality, and b) moderate impostor feelings (41-60), frequent impostor feelings (61-80), and intense impostor feelings (≥81).

Discussion

The prevalence of depression in this sample is higher than is typically reported in the general population but lower than medical students in previous studies (i.e., 27%-58%) (Dyrbye et al., 2014; Rotenstein et al., 2016). In contrast, the prevalence of SI in this sample is higher than is reported in both the general population and medical students in previous studies (i.e., 9%-11%) (Dyrbye et al., 2014; Rotenstein et al., 2016). Additionally, approximately one-third of medical students in this sample had a history of suicidality (SI or suicide attempt), which may suggest that at-risk individuals are self-selecting into the medical field. This may partially explain the disparity in physician suicide relative to the general population. Alternatively, this could be an indication of how arduous the path to a career in medicine can be. Longitudinal research is needed to examine the temporality of these relations in order to develop appropriate intervention approaches.

Risk factors that appear to be most salient in this study include sleep quality, impostor feelings, stress, and to some extent, financial distress. Impostor feelings were associated with every mental distress indicator in this study. Individuals with impostor syndrome constantly doubt their skills and abilities, and are often fearful of being discovered as an impostor, or as someone who does not belong (Villwock et al., 2016). This sample also had a very high prevalence of impostor feelings relative to other studies. A recent review of impostor syndrome in medical students cites prevalence among studies between 20-60% (Gottlieb et al., 2020). Coping with feelings of impostor syndrome in medical students has not been explored in the literature. A study addressing the impostor phenomenon in academic faculty suggests that increasing formal institutional support (e.g. professional development, mentorship, and teaching active coping strategies) and increasing the use of peer support networks may decrease feelings of impostor syndrome (Hutchins & Rainbolt, 2017).

The results of this study add to the literature showing that poor sleep quality is associated with depression and suicidality (Grady & Roberts, 2017; Russell et al., 2019; Wolf & Rosenstock, 2017), indicating that improved sleep behaviors should be emphasized for medical students and supported by the larger medical school context. The burden of this not only lies with the student, but also extends to institutional levels and should be seriously considered during curriculum development and implementation. Stress was found to be another modifiable risk factor for depression in medical school. Although much attention has been devoted toward development of stress reduction programs for medical students [e.g. through mindfulness (Daya & Hearn, 2018; De Vibe et al., 2013; Yang et al., 2018) and coping (McGrady et al., 2017) interventions], these programs are not adapted by every institution. There are also mixed findings on the effectiveness of these interventions. Some report reductions in stress and anxiety and

increases in self-efficacy (Daya & Hearn, 2018; McGrady et al., 2017), while others report no effect on stress, mental quality of life, or depression (Brennan et al., 2016; Daya & Hearn, 2018; Dyrbye, Shanafelt, et al., 2017). Further, demanding schedules during medical training may not easily allow for time to fully engage in stress reduction training programs. The results of this study show that stress is indeed associated with a positive DS in medical students, and efforts should be made by future stress intervention programs to target depression.

Financial distress was associated with depression in this sample. This potential risk factor for mental distress may become more salient in the coming years for medical students as medical schools work toward expanding the physician workforce to include people from economically disadvantaged backgrounds (Kalter, 2018). This means that the percentage of matriculants coming from the lower three quintiles of household income is likely to increase, which means that a higher percentage of medical students will need financial support. Additional research is needed to investigate financial distress in medical students, with the long-term goal of affecting policy that would support medical students that do not come from affluent homes. All medical students, regardless of background, should be able to focus on navigating the rigorous medical curriculum without having to worry about how they will pay their monthly bills.

Although hazardous alcohol use was not associated with depression or suicidality in this study, the fact that half of the sample screened positive for hazardous drinking is concerning. A nationwide study of physicians found that 12.9% of male physicians and 21.4% of female physicians screened positive for alcohol mis-use (Oreskovich et al., 2015). Although the prevalence was much higher in this study sample, I see the same trend of more female medical students screening positive for hazardous drinking. This also may be due to the fact that the screen used to assess hazardous alcohol use has a lower cut-off for females (see the methods

section). High alcohol use is associated with depression, SI, low quality of life, recent medical errors, and suicide in physicians and should be treated seriously in medical students (Bright & Krahn, 2011; Oreskovich et al., 2015). Given the temporal context of when participants were assessed (e.g., early in their careers during medical school), high alcohol use may emerge as a significant risk factor for depression and suicide later in their career.

Limitations

Due to the cross-sectional nature of this study, the findings cannot speak to the temporality of the development of depression and suicidality. These findings may also not be generalizable to all medical students because this study incorporated only one medical school, however, this sample had greater racial and ethnic diversity than what is seen in medical students at the national level (Association of American Medical Colleges, 2020).[2] Future studies should incorporate multiple institutions to both increase sample size and generalizability. Another limitation is that the survey was not truly anonymized in that the design of the study involved an in-person appointment with one member of the research team. Because mental health is stigmatized in this population, the data may be subject to a social desirability effect. Future studies should aim to make survey collection anonymous to ensure participant comfort.

Strengths

This comprehensive study investigated a broad range of risk factors for depression and suicidality in medical students early in training. My findings of high prevalence of depressive symptoms and suicidality in this sample supports the importance of early intervention during

[2] According to the Association of American Medical Colleges, among all medical students enrolled in 2019, 50% were White, 22% were Asian, 7% were Black, and 6% were Hispanic/Latino origin.

medical training. This study is the first of its kind to assess the prevalence of suicidal history in medical students. The high prevalence of suicidal history in this sample suggests that medical students may be at increased risk for suicide even before entering medical school (i.e., especially for students in their first year of training that reported a suicidal history). Longitudinal and qualitative studies are needed determine at what point suicidality develops in (pre)medical students, and for what reason(s). This study is also the first to consider financial distress during medical school as a potential risk factor for depression and suicidality in this population. The finding that depression is associated with difficulty paying monthly bills highlights the need for future studies to examine this relationship through the lens of a more detailed survey of socioeconomic variables.

Implications

These novel findings suggest that targeted interventions should aim at improving sleep, reducing stress and impostor syndrome, and eliminating financial insecurity in medical students. Discussions of the implications of impostor syndrome should be had amongst medical school administration, faculty, and attending physicians. Efforts should be made at the institutional level to hire individuals who are committed to nurturing the confidence and careers of our future healers. Further research efforts on impostor syndrome are needed to explore potential intervention strategies. Future intervention studies should also target the effect of structural changes (i.e. reducing weekly mandatory class or clinic hours to promote healthy sleep behaviors and stress reduction) on mental distress in medical students. Longitudinal studies are also needed to determine whether the risk factors outlined in this study precede depression and suicidality in medical students. These studies may elucidate a potential causal pathway for the development of

mental distress in medical students, which will inform intervention studies with the long-term goal of influencing policy to better support medical student mental health and wellness.

CHAPTER 3
Hypothalamic-Pituitary-Adrenal Axis Activity and Mental Distress among Medical Students

Medical students experience heightened rates of depression and thoughts of suicide (i.e. suicidal ideation) relative to the general population (Dyrbye et al., 2014). Despite higher rates of mental distress, they are less likely than the general population to seek help (Dyrbye et al., 2015). This lack of help-seeking behavior results, in part, from the profound mental health stigma in the medical field (Adams et al., 2010; Bartlett & Fowler, 2019; Chew-Graham et al., 2003; Givens & Tjia, 2002; J. A. Gold et al., 2015; K. J. Gold et al., 2016; Hassan et al., 2009; Kuhn & Flanagan, 2017; Moutier, 2018; Schwenk et al., 2008, 2010). This stigma may prevent students from taking signs of mental distress within themselves seriously (Bartlett & Fowler, 2019; K. J. Gold et al., 2016). Given the potential stigma-induced barriers to obtaining support for mental health, it is important for this population to have a mechanism through which members can better understand the severity of their symptoms and their downstream effects. Having access to a biological, objective measure of depression and suicide risk may assist this population in moving past stigma and addressing their need for medical help. With this long-term goal in mind, this study examines the use of salivary biomarkers as potential early indicators of depression and suicide risk.

There is evidence that biomarkers of the hypothalamic-pituitary-adrenal (HPA) axis are associated with depression, SI, and suicide attempt (Adam et al., 2017; D. B. O'Connor et al., 2016; Wasserman et al., 2010). The HPA axis regulates function across several different systems, including the neuroendocrine, immune, and metabolic systems (Silverman & Sternberg, 2012). HPA axis activation results in the release of cortisol, a glucocorticoid, from the adrenal glands. Cortisol levels follow a diurnal (i.e. daily) rhythm (Adam et al., 2017) that is

characterized by high waking levels that peak approximately 30 minutes after waking, followed by a decline throughout the day with an evening nadir (J. C. Pruessner et al., 1997). Stress-related HPA axis activation also results in increases in cortisol concentration throughout the body (P. W. Gold & Chrousos, 2002). Cortisol is independently associated with depression and suicidality. High diurnal cortisol is associated with depression in adolescents, adults, and older adults (Bremmer et al., 2007; Pariante & Lightman, 2008; Veen et al., 2011). The cortisol awakening response (CAR) is also associated with depression, although findings are mixed. Most studies report higher CAR in individuals with depression (in adolescents, adults, older adults), but some studies have also reported an association between blunted CAR and depression (in adolescents and adults), and no association between CAR and depression (in adolescents) (Dedovic & Ngiam, 2015; Knorr et al., 2010; Shibuya et al., 2014; Stetler & Miller, 2011). The diurnal slope of cortisol has also been associated with depression, but findings are again inconsistent. Depression has been associated with a steeper diurnal slope in adult psychiatric outpatients (Veen et al., 2011), while meta-analysis finds an association between flatter slope and depression (Adam et al., 2017). Taken together, these findings suggest that depressive symptoms are associated with dysregulation of the HPA axis, however the directionality of the association is unclear.

Cortisol concentrations are also associated with lifetime history of suicidality (O'connor et al., 2020). In a community sample of adults ages 18 to 63, those with a history of suicide attempt or SI had significantly lower CAR and flatter wake-peak to 12 hour slopes compared to those with no history of suicidality (O'connor et al., 2020). Additionally, lower baseline plasma cortisol is associated with personal and family history of suicidal behaviors (McGirr et al., 2011), and salivary cortisol is lower in suicide attempters relative to those with thoughts of suicide, and

those without a suicidal history (Melhem et al., 2016). A recent study examined temporality of HPA axis activity relative to suicide attempt or SI by analyzing cortisol in scalp hair. Cortisol concentrations were lower in the hair of first time suicide attempters relative to individuals with SI without attempt, and healthy controls (Melhem et al., 2017). The current literature suggests that lower cortisol is associated with multiple indices of suicidality (e.g. suicide attempt, SI, and history of suicidality). Gaps in our knowledge regarding the associations between HPA axis function and mental distress remain, including the extent to which cortisol is dysregulated in early depression and suicidality in young adults and the directionality of associations (i.e. high versus low cortisol output), especially in the context of a high stress population, such as medical students.

I begin to address these questions by assessing relations between indicators of mental distress (depression, SI, suicide risk, and history of suicidality), and: 1) diurnal cortisol output and 2) the slopes of the morning rise and daily fall of cortisol in a sample of young, moderately healthy medical students. I hypothesize that higher diurnal cortisol output will be associated with a positive depression screen, and that lower diurnal cortisol will be associated with SI, suicide risk, and history of suicidality. I also hypothesize that higher scores on all measures of mental distress will be associated with a flatter diurnal cortisol slopes (i.e., smaller morning rise and less steep daily fall).

Methods

Study design and participants

All students enrolled in a large, southern California medical school from 2018-19 were invited to participate in this study via in-person and email announcements. Exclusionary criteria included chronic medical conditions related to inflammation (i.e., asthma, arthritis, cardiovascular disease, cancer), or related to cortisol production (i.e., Cushing's syndrome or Addison's disease), current illness (i.e., upper respiratory infection), periodontitis, oral sores or injuries, use of anti-inflammatory or corticosteroid medications, and pregnancy. After completing informed consent procedures, participants were asked to complete an in-person survey containing sociodemographic questions and validated measures of depression and suicidality. Participants also completed two consecutive days of passive drool saliva collection at home. Samples were collected at waking, 30 minutes after awakening, noon, and bedtime each day. This timing allows us to approximate the diurnal cortisol curve (J. C. Pruessner et al., 1997). Participants received verbal and written saliva collection guidelines and were asked to record sample collection times and any medications taken on the day of collection. Participants were asked not to eat, drink, or brush their teeth prior to collection, to collect on two consecutive weekdays if possible, and to follow the storage and transport guidelines. Participants were compensated $50 upon completion in the study. Study participation was voluntary, and all survey responses were anonymized. Study and recruitment procedures and materials were approved by the University's Institutional Review Board prior to recruitment.

Measures

Depression Screen

Responses on the Patient Health Questionnaire-9 (PHQ-9) were used to assess depressive symptom severity in the past two weeks. The PHQ-9 focuses on the nine DSM-IV diagnostic

criteria for depressive orders (Kroenke & Spitzer, 2002). The PHQ-9 has good reliability (Cronbach's alpha values range from 0.86-0.89) and has been validated for use in student and general population samples (Kroenke et al., 2001). PHQ-9 scores range from 0-27 with a cut-off score of 10 recommended as a threshold for identifying individuals experiencing major depressive disorder with 88% sensitivity and 88% specificity (Kroenke et al., 2010). Here we refer to this cut-off as a positive depression screen (DS), and we use this as a dichotomous variable in analyses.

Suicidality

Responses on the Suicidal Behaviors Questionnaire-Revised (SBQ-R) were used to assess three indicators of suicidality: SI in the previous 12 months, lifetime suicidal thoughts and behaviors, and overall suicide risk based on global scores. The SBQ-R is validated for use in college students and in the general population with good reliability (Cronbach's alpha values ranging from 0.76-0.87). Scores range from 3-18 with a cut-off score of 7 having optimal sensitivity (93%) and specificity (95%) to differentiate between non-suicidal and suicidal individuals (Osman et al., 2001). All three indicators of suicidality were used as dichotomous variables created using established cut-offs (Osman et al., 2001).

HPA Axis Function

Salivary cortisol was used as a measure of HPA axis function. Salivary cortisol concentrations are strongly correlated with serum cortisol concentrations (Kirschbaum & Hellhammer, 1994) and salivary cortisol is a validated measure of serum levels (Adam & Kumari, 2009; Hellhammer et al., 2009). Cortisol was assayed from all 8 samples of whole

saliva and tested in duplicate using a commercially available enzyme-linked immunoassay (ELISA) kits (Salimetrics CAT# 1611550). The test volume was 25 μL with a range of standards from 0.012 – 3.0 μg/dL, and the assay had a lower limit of detection of 0.007 μg/dL. Samples were assayed following manufacturer instructions (Salimetrics, 2018). The total average inter-assay coefficient of variation (CV) was 6.04% and the average intra-assay CV was 5.99%.

Covariates

In adjusted models, we controlled for self-reported variables that are known correlates of cortisol concentrations when measured in oral fluids. These included sex, age, oral health indices (e.g. bleeding gums during teeth brushing as a measure of gingival health), use of anti-inflammatory or corticosteroid medications, and type of day (e.g. weekday saliva collection or weekend day saliva collection) (Dedovic & Ngiam, 2015; Hansen et al., 2008; Hellhammer et al., 2009; Refulio et al., 2013). We did not control for smoking tobacco products because all participants reported not smoking.

Analysis Plan

To examine associations between mental distress and diurnal cortisol output (research question 1), we used a linear multilevel modelling approach with cortisol concentration as the outcome variable. Cortisol was log-transformed to achieve normality, and the results were back-transformed through exponentiation to assist interpretation.[3] Best model fit was confirmed through residual diagnostics, likelihood-ratio tests, and information criteria. Sensitivity analyses

[3] We acknowledge that there is a back-transformation bias and that exponentiating log-transformed estimates results in the geometric, and not arithmetic mean (Miller, 1984). We interpret the geometric mean as the median here because we are assuming that our data is log-normal based on the normalized plots of the log-transformed data (Shih & Binkowitz, 1987).

were also performed to assess the effect of extreme cortisol concentrations on the model fit and estimated parameters by evaluating model significance and information criteria.

Three-level multilevel models were structured with: level 1) the saliva samples; level 2) the day of sampling; and level 3) the person. Four separate models were conducted to test the independent associations between each mental distress indicator, DS, SI, suicide risk, and history of suicidality (the main independent variable), and salivary cortisol (the dependent variable). For each model, we began with a base model that included only the log-cortisol outcome and the mental distress indicator (e.g., DS) to assess bivariate associations. This base model included random intercepts at the second and third levels, which allowed the cortisol intercepts to vary across sample days and between person. We then added a spline knot at the second sample of the day, which enabled the model to analyze the two slopes of the diurnal curve separately (see Figure 1 for a raw data plot). In this stage, the two slope terms were added to the model as additional covariates only. Next, we introduced random slopes for both spline terms in the third-level of the model, which essentially allowed the two cortisol slopes to vary between person. In our final stage of model building, we added conceptually important covariates controlling for sex, weekday vs. weekend day of sample collection, oral health, and medication use. Bivariate associations between log-transformed cortisol and each covariate were assessed in the final model, but covariate choice was driven by the literature. Intraclass correlation coefficients (ICCs) and variance partition coefficients (VPCs) were calculated to determine the variation in cortisol at each level.

To address research question 2, we included an interaction term in each final model between the mental distress indicator (e.g., DS) and 1) the slope of the morning rise of cortisol,

and, in a separate model, 2) the slope of the daily fall of cortisol. All analyses were run using Stata/SE 15.1.

Results

Table 1. Sample Characteristics		
		n (%)
Sex	Male	53 (48.18)
	Female	57 (51.82)
Age (years)	22-24	40 (36.36)
	25-27	49 (44.54)
	28-30	19 (17.27)
	31-33	1 (0.9)
	34-37	1 (0.9)
Race	Asian	52 (47.27)
	White	49 (44.55)
	Other/Prefer not to answer	9 (8.18)
Hispanic/Latino origin	Yes	16 (14.95)
	No	91 (85.05)
Depression screen (DS)	Positive	19 (17.27)
	Negative	91 (82.73)
SI in the previous 12 months	Yes	20 (18.18)
	No	90 (81.82)
Suicide risk screen	Positive	12 (10.91)
	Negative	98 (89.09)
History of suicidality	Yes	38 (34.55)
	No	72 (65.45)
Bleeding gums [a]	Yes	17 (15.45)
	No	93 (84.55)
Ibuprofen or naproxen use [b]	Yes	54 (49.09)
	No	56 (50.91)

[a] Participants were asked if their gums bleed when they brush their teeth.
[b] Those who responded "yes" take ibuprofen or naproxen weekly as needed.

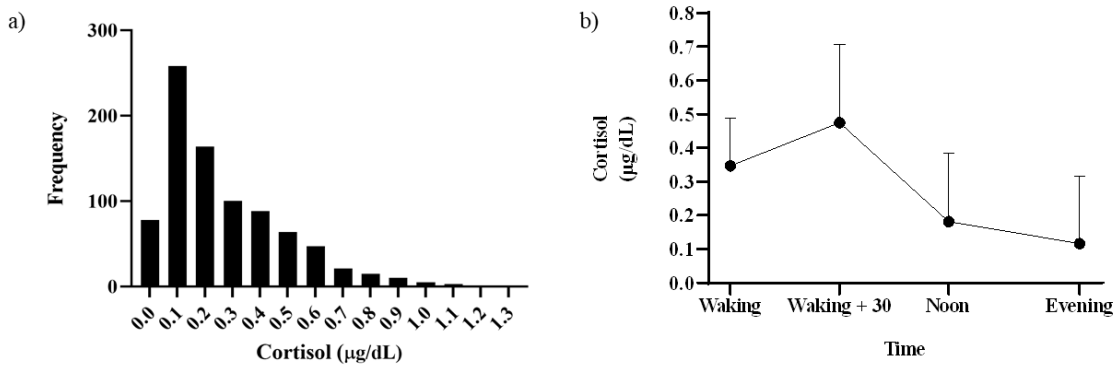
Preliminary Analyses

Saliva samples were returned by 109 (81.3%) of the 134 medical students enrolled in the study. There were no significant differences in demographic characteristics or mental distress indicators between those who returned saliva samples and those who did not. The majority of saliva samples were collected on weekdays (77.52% (676/872)). Sex was the only statistically significant demographic or health characteristic in all models. Table 2 includes descriptive statistics for raw cortisol.

Table 2. Descriptive Statistics of Raw Cortisol

Cortisol (μg/dL)	n	Mean	Median	SD	Min	Max
Day 1						
Awakening	108	0.321	0.286	0.173	0.040	0.881
Awakening+30 min	107	0.493	0.459	0.256	0.013	1.720
Noon	107	0.189	0.130	0.230	0.022	2.020
Evening	109	0.116	0.072	0.184	0.004	1.366
Day 2						
Awakening	107	0.377	0.353	0.190	0.010	1.036
Awakening+30 min	107	0.452	0.408	0.250	0.038	1.538
Noon	107	0.161	0.143	0.096	0.018	0.610
Evening	109	0.115	0.088	0.251	0.017	2.641
Mean						
Awakening	108	0.347	0.341	0.141	0.025	0.818
Awakening + 30	107	0.475	0.447	0.232	0.053	1.367
Noon	107	0.182	0.144	0.202	0.020	2.015
Evening	109	0.116	0.074	0.199	0.019	1.961

Figure 1. Distribution and Diurnal Output of Raw Cortisol



The frequency distribution of raw cortisol concentrations across all sampling timepoints is represented by plot a. Mean raw diurnal cortisol concentrations averaged across two days, including standard deviations, is represented by plot b. Raw cortisol was log-transformed in analyses. Skewness and kurtosis for raw cortisol was 2.52 and 16.16, respectively. Skewness and kurtosis for log-transformed cortisol was -0.39 and 2.84, respectively.

Salivary Measurement Quality Controls and Missingness

A total of 873 saliva samples were assayed for cortisol. If determinations had a CV >15% *and* an absolute difference between duplicate concentrations <0.030 µg/dL, the sample was retested in duplicate (Salimetrics, 2018). If the retest result maintained a CV >15%, the sample cortisol concentration was changed to missing. If determinations had a CV >15% *and* an absolute difference ≥0.030 µg/dL they were changed to missing. Twelve concentrations (1.2% (11/873)) were changed to missing using these criteria. One sample had a cortisol concentration that was above the upper limit of sensitivity of the assay (ULOS) and was changed to missing after the retest remained ULOS after dilution, suggesting assay interference. No concentrations were below the lower limit of detection (LLOD). Overall, 13 determinations were dropped from the dataset (1.4% (13/873)), leaving 861 cortisol estimates to be included in analyses.

We classified extreme values as being ≥4 standard deviations above the mean. We identified 8 cortisol concentrations as extreme values and dropped these individual sample

determinations from the analytic dataset because sensitivity analyses revealed better model fit when these samples were dropped.

The results are presented such that we can observe differences in estimates and significance values through each stage of model building.

Table 3. Maximum likelihood estimates for daily cortisol output and suicide risk data (log-transformed)

	Base model				Spline covariate model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive SBQ]	0.20264	0.112	-0.0472978	0.45258	0.21683	0.094	-0.03656	0.47022
β2 [Sampletimepre30]	-	-	-	-	0.00270	0.126	-0.00076	0.00615
β3 [Sampletimepost30]	-	-	-	-	-0.00256	0.000	-0.00273	-0.00238
β4 [Female]	-	-	-	-	-	-	-	-
β5 [Daytype]	-	-	-	-	-	-	-	-
β6 [Bleeding gums while brushing]	-	-	-	-	-	-	-	-
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-	-	-	-
log-likelihood	-1149.95				-830.88			
AIC	2309.90				1675.75			
BIC	2333.65				1709.00			
ICC| person level	0.0772		0.0385	0.1488	0.2809		0.2107	0.3637
ICC| sample day level	0.0772		0.0385	0.1488	0.2809		0.2107	0.3637

	Spline slope model				Full model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive SBQ]	0.23611	0.062	-0.01173	0.48394	0.26307	0.0410	0.01072	0.51541
β2 [Sampletimepre30]	0.00313	0.07	-0.00026	0.00652	0.00329	0.0600	-0.00014	0.00672
β3 [Sampletimepost30]	-0.00261	0.000	-0.00283	-0.00239	-0.00262	0.0000	-0.00282	-0.00234
β4 [Female]	-	-	-	-	0.19839	0.0130	0.04145	0.35533
β5 [Daytype]	-	-	-	-	-0.07023	0.2900	-0.20025	0.05979
β6 [Bleeding gums while brushing]	-	-	-	-	0.20364	0.0610	-0.00958	0.41686
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-0.10374	0.2180	-0.26890	0.06142
log-likelihood	-814.32				-791.96			
AIC	1652.64				1615.91			
BIC	1709.64				1691.61			
ICC| person level	0.2891		0.1757	0.4368	0.2855		0.1710	0.4362
ICC| sample day level	0.2891		0.1757	0.4368	0.2855		0.1710	0.4362

Associations between DS, SI, suicide risk, and history of suicidality, and diurnal cortisol output

Model results are presented in tables as log-transformed estimates, but the figures discussed in the text have been back-transformed via exponentiation to assist interpretability. Note that because the estimates were exponentiated, confidence intervals containing 1 are not significant.

Depression Screen

DS was not significantly associated with diurnal cortisol output in this sample (Appendix A). Sex was significantly associated with daily cortisol output. The median daily cortisol output was 21% higher in females relative to males ($\beta = 1.21$, $p = 0.02$, 95% CI: 1.02 – 1.43).

Suicide Risk

Suicide risk was significantly associated with diurnal cortisol output (Table 3). Median cortisol output was 30% higher in those with a positive suicide risk score relative to those with a negative suicide risk score (Figure 2). Sex was also associated with cortisol output, where females had a median daily cortisol output that was 21% higher than males.

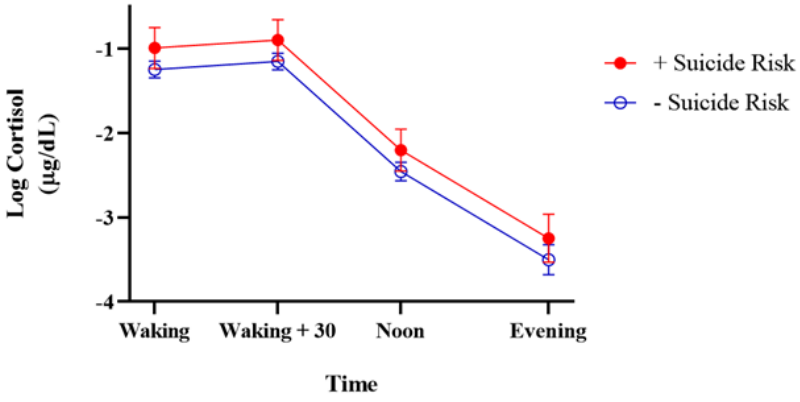
Suicidal Ideation

SI was not significantly associated with daily cortisol output in this sample.

History of Suicidality

History of suicidality was not significantly associated with daily cortisol output, although there may be a trend suggesting higher median diurnal cortisol output in those with a history of suicidality relative to those without a history of suicidality ($\beta = 1.16$, $p = 0.06$, 95% CI: -0.008 – 0.313) (Appendix A).

Figure 2. Diurnal Log Cortisol Output by Suicide Risk



Associations between DS, SI, suicide risk, and history of suicidality, and slopes of the morning rise and daily fall of cortisol

Depression screen

The interactions between DS and the slope of the morning rise of cortisol and DS and the slope of the daily fall of cortisol were not statistically significant (Appendix A).

Suicide risk

The interactions between suicide risk and the slope of the morning rise of cortisol and suicide risk and the slope of the daily fall of cortisol were not significant. However, the suicide risk predictor remained significant in both slope interaction models (morning rise: $\beta = 1.43$, $p = 0.026$, 95% CI: 1.04 – 1.97; daily fall: $\beta = 1.32$, $p = 0.043$, 95% CI: 1.01 – 1.74) (Appendix A).

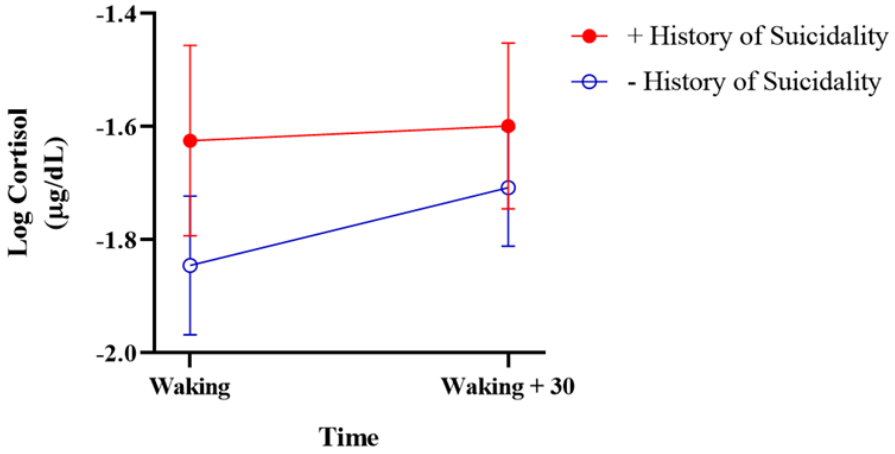
Suicidal ideation

The interactions between SI and the slope of the morning rise of cortisol and SI and the slope of the daily fall of cortisol were not significant (Appendix A).

History of suicidality

The interactions between history of suicidality and the slope of the morning rise of cortisol, and history of suicidality and the slope of the daily fall of cortisol were not significant (Appendix A). However, the history of suicidality predictor was positive and significant in the presence of an interaction in the morning slope interaction model (β = 1.23, p = 0.04, 95% CI: 1.01 – 1.51) (Figure 3).

Figure 3. History of Suicidality and Morning Cortisol Slope Interaction Plot



The parallel lines indicate no interaction between history of suicidality and morning cortisol slope. However, median cortisol output is statistically significantly higher among those with a history of suicidality.

Interclass correlations for cortisol

Interestingly, the conditional interclass correlations (ICC) for all models were exactly the same between the person level and sample day levels. To investigate this further, we calculated the variance partition coefficients (VPC) at each level of the depression screen model and found

that 29% of the variation in cortisol lies between person, 0% of the variation lies between sample days, and 70% of the variation lies between samples. In the SI model, 28% of variation was between person, 0% between sample days, and 71% between samples. In the suicide risk model, 27% of variation was between person, 0% between sample days, and 72% between samples. And lastly, in the history of suicidality models, 27% of variation was between person, 0% was between sample days, and 72% between samples.

Discussion

This study explored salivary cortisol as a potential early indicator of depression and suicide risk in a sample of healthy medical students. The overarching goal of this research study is to advance science that could eventually enable the use of biomeasures to predict risk and/or severity of illnesses like depression and suicidality before clinical presentation, and as a tool to inform, monitor, and evaluate intervention and prevention efforts (Boksa, 2013).

In this study, suicide risk was significantly associated with cortisol output. Those at risk for suicide had a 31% higher daily cortisol output than those not at risk. Although previous studies have not focused specifically on the suicide risk construct, our finding is in contrast to the low cortisol state that is observed in suicide attempt, SI, and history of suicidality. Medical students are often chronically stressed, and this may be influencing the directionality of the findings (Rotenstein et al., 2016). History of suicidality may also be associated with higher cortisol output, but we are interpreting this finding with caution because the association was not statistically significant in the absence of a morning slope interaction. The directionality of this

association also contrasts with previous research. There is evidence that age might be moderating this association, given that the average age of this sample was 25 years. According to meta-analysis, hyperactivity of the HPA axis is associated with suicide attempt in people under the age of 40, and hypoactivity of the HPA axis is associated with suicide attempt in people over the age of 40 (D. B. O'Connor et al., 2016).

Diurnal cortisol output was not associated with DS, SI, or history of suicidality in this sample. These nonsignificant findings may be due in part to the fact that this is a young and moderately healthy sample. Additionally, participants in our study were able to choose the day of at-home saliva collection. We did not collect information on perceived stress or mood on the days of saliva collection, but we assume that participants chose a relatively low-stress day to collect the samples in between academic and clinical responsibilities. The potential low-stress and basal conditions under which samples were collected could explain some of the nonsignificant findings. This sample is also habituated to a rigid daily schedule, and it is possible that their diurnal cortisol levels are responsive to daily medical school demands, which may confound associations between cortisol output and mental distress.

It is also possible that we did not observe a significant association between cortisol output and depression because we only screened for depression and did not include a clinical assessment nor diagnosis. This means that we cannot confirm a clinical depression presentation among our participants (only self-reported depressive symptoms) and we cannot delve into the many sub-types of major depression. For example, atypical depression, which makes up an estimated 15-30% of cases of major depression, is associated with a hypoactive stress response (Lamers et al., 2013; Stetler & Miller, 2011). This is in contrast to melancholic depression, which makes up 25-30% of cases of major depression, and is associated with a hyperactive stress

response (P. W. Gold & Chrousos, 2002; Lamers et al., 2013; Stetler & Miller, 2011). These depression subtypes also vary in their clinical presentation. Atypical depression is characterized by mood reactivity with the addition of at least two of the following symptoms: increased appetite and weight gain, hypersomnia, severe fatigue referred to as leaden paralysis, and interpersonal rejection sensitivity (American Psychological Association (APA), 2013). While, melancholic depression is characterized by decreased appetite, variability in mood based on the time of day, lack of energy, insomnia, and feelings of worthlessness (American Psychological Association (APA), 2013).

Assessing differences in HPA axis function across depression subtypes may require a pharmacologic challenge (Juruena et al., 2018). For example, Dexamethasone suppresses cortisol production by reducing hypothalamic output of corticotropin releasing hormone (CRH) (Brown, 2012). Suppression of cortisol following dexamethasone administration is indicative of a normally functioning HPA axis (Brown, 2012). Melancholic depression, compared to atypical depression and controls, shows high cortisol concentration after a Dexamethasone suppression test (Juruena et al., 2018). Dexamethasone suppresses cortisol production by reducing hypothalamic output of corticotropin releasing hormone (CRH). Suppression of cortisol following dexamethasone administration is indicative of a normally functioning HPA axis. Future studies should include clinical evaluations of depressive disorders and assess the different subtypes of depression potentially with a stress challenge. We also recommend that future studies have a longitudinal design to assess changes in neuroendocrine dysregulation in medical students as they progress through training.

Limitations

While our findings are encouraging, there are several limitations that warrant discussion. Due to the cross-sectional study design we could not examine the temporal association between HPA axis dysregulation and indices of suicidality. Another limitation is that we were underpowered due to small sample size to investigate associations between cortisol and mental distress separately by sex which was significantly associated with cortisol in all of our models and may be a significant moderator of the relations examined (Hansen et al., 2008; Juster et al., 2016). We also did not collect information on mood or stress experienced on the days of saliva collection, which could confound or mediate the significant associations found in this study. We also know that mental health is stigmatized in this population, and participants completed the survey in the same room as a member of the research team. Future studies should ensure more privacy and ideally, complete anonymity potentially through an online survey. Although at-home saliva collection is non-invasive and convenient for the participant, we are relying on the accuracy of the participant's sample collection time diary and on their compliance with sample storage and transport guidelines (i.e. we do not have information about the cold-chain prior to the samples being returned). Collecting saliva samples in a controlled, laboratory environment would mitigate these issues.

Strengths

Although it has its limitations, at-home saliva collection is also a strength of this study. Participants collected saliva at home which is likely much less stress-inducing and more ecologically-valid than collecting the saliva in a laboratory environment. Even under these low-stress conditions, we observed associations between suicide risk, history of suicidality, and cortisol output, suggesting a potentially meaningful association between these measures of mental distress and HPA function. The study findings are also supported by a robust data

collection protocol that included multiple saliva samples per day on two separate days. Salivary cortisol measurements are variable across days and collection times, and our collection protocol minimizes this variance in order to look at more trait-like cortisol profiles. Finally, this study adds to a small, yet essential, area of research into the health and well-being of medical professionals. Our sample is unique in its focus on medical trainees and the biopsychosocial processes underlying health in this important population.

Implications and Conclusions

The results of this study indicate that the HPA activity is increased in young individuals at risk for suicide. Additional research is needed to examine this association. Future research should collect data longitudinally to assess temporality of findings, include a larger sample size of high-risk individuals, potentially stratify analyses by sex, include a clinical diagnosis of depression as opposed to a screen, and incorporate a multisystem assessment to gain further insight into the pathophysiology of suicidality. In addition to differential presentation of biomeasures by depression subtypes, there are inherent individual differences in how the biomarkers correlate with disease states, supporting the need for future research that is more clinical in nature.

CHAPTER 4
Exploratory Analyses of Neuroendocrine-Immune Coordination and Mental Distress among Medical Students

This chapter builds on the preceding chapter by taking a multisystem approach to understanding the biological underpinnings of mental distress. In a series of exploratory analyses, I build an emerging area of investigation to evaluate coordination between hypothalamic-pituitary-adrenal axis (HPA) and inflammatory function and the risk for depression and indices of suicidality in medical students. In this chapter, I explore associations between inflammation and indicators of mental distress, as well as the interaction of the HPA axis and inflammatory activity and how this relates to indicators of mental distress in this sample of young medical school students.

There is a rich body of literature suggesting that immune dysregulation is involved in the pathophysiology of depression and suicidal thoughts and behaviors (i.e. suicidality). For example, increased plasma concentrations of proinflammatory cytokines (interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α)) are observed in individuals with depression (Dowlati et al., 2010) and in individuals who have thought about or attempted suicide (Black & Miller, 2015) when compared to healthy controls. Post-mortem suicide studies have also observed elevated expression of cytokines in areas of the brain that are thought to be associated with suicidality, the dorsolateral prefrontal cortex and orbitofrontal cortex (Pandey et al., 2012; Tonelli et al., 2008).

C-reactive protein (CRP), an acute phase protein released by the liver in response to systemic inflammation (S. Black et al., 2004), is positively associated with depression (Valkanova et al., 2013). In a study of depressed psychiatric inpatients, serum CRP levels were positively associated with a history of suicide attempt and the risk of suicide attempt increased as

CRP levels increased in a dose-response fashion. Additionally, patients with a history of suicide attempt were twice as likely to have high levels of CRP compared to patients without history of suicide attempt (Courtet et al., 2015). Higher serum CRP concentrations have also been observed in suicide attempters relative to those who have SI but have not attempted suicide (Melhem et al., 2017). There is also evidence of differences in inflammation among individuals with high and low SI. Depressed inpatients with high SI had a higher inflammatory index (composite variable encompassing plasma concentrations of TNF-α, IL-6, IL-10, CRP) than depressed inpatients with low SI (O'Donovan et al., 2013). What is not known, is the extent to which CRP is associated with depression and indices of suicidality in early stages of these disorders. What is also not explored in the literature is the association of CRP with depression and suicidality at different times across the day, and the change of CRP across the day (i.e. diurnal slope). CRP is thought to peak upon waking and decrease throughout the day (Izawa et al., 2013), similar to the diurnal pattern of cortisol (i.e. morning high and decrease throughout the day) (Kirschbaum & Hellhammer, 1994), and cortisol and CRP have been shown to interact – hinting at the importance of coordinated diurnal function across both the HPA and inflammatory systems.

Immune dysregulation (e.g. overproduction of cytokines and CRP), is also associated with dysregulation of the hypothalamic pituitary adrenal (HPA) axis due to the bidirectional feedback loop between these systems (McEwen, 1998; Silverman & Sternberg, 2012). In response to a stressor, the hypothalamus releases corticotropin-releasing hormone (CRH), which signals the anterior pituitary to release adrenocorticotropin (ACTH), which in turn stimulates the adrenal glands to secrete cortisol (CORT) (Silverman et al., 2003; Silverman & Sternberg, 2012). Proinflammatory cytokines (e.g. TNF-α, IL-1, IL-6) stimulate each level of the HPA axis, and in a homeostatic system, cortisol acts to suppress immune activity and each level of the HPA axis

(Silverman et al., 2003). Dysregulation of this feedback loop between the HPA axis and immune system is associated with depression (Pariante & Lightman, 2008). And more recently, the literature has highlighted an association between this dysregulation and suicide attempt in clinical populations (Courtet et al., 2016). Similar to the research examining CRP and mental distress, little is known about the extent to which this neuroendocrine-immune (NEI) dysfunction is present in the early stages of depression and suicidality. Only one study was identified that examined these relations in a non-clinical sample. This study found that, among healthy participants with no history of depression, higher depressive symptoms was associated with a low ratio of cortisol/CRP (CORT/CRP) in women. These findings suggest early involvement of NEI dysfunction (Suarez et al., 2015) in depressive symptomatology.

In this study, I build on this growing body of research into the role of NEI coordination and CRP in depression and suicidality. This study begins to address important gaps in the understanding of inflammatory and NEI dysfunction and mental distress in a non-clinical sample of young adults assessed in both the morning and evening. Using salivary indicators of HPA and inflammatory function across the day, I address the following research questions:

1) Are there associations between indicators of mental distress (e.g. positive depression screen (DS), SI, suicide risk, and history of suicidality) and: a) waking CRP concentrations?; b) evening CRP concentrations?; and c) the trajectory of CRP change across the day (i.e., CRP diurnal slope)? Due to innate differences in CRP between males and females, I assessed these associations separately by sex in preliminary analyses (Lakoski et al., 2006; Vetter et al., 2013).

I hypothesize that a positive DS and all measures of suicidality will be associated with higher waking and evening levels of CRP, and a flatter slope of CRP change across the day.

2) Are there associations between indicators of mental distress and NEI dysfunction as measured by: a) the CORT/CRP ratio at waking and in the evening?; b) the interaction between CRP and cortisol diurnal slopes?; and c) the interaction between total diurnal output of CRP and cortisol?

I hypothesize that a positive DS and all measures of suicidality will be associated with a high CORT/CRP state, flatter diurnal slopes, and high cortisol and CRP output. I expect to see an association between all indicators of mental distress and both the interaction of daily outputs and interaction of diurnal slopes, although I acknowledge that this sample is young, non-clinical, and that the associations may not be apparent at this stage (Cubała & Landowski, 2014).

Methods

Study design and participants

All students enrolled in a large, southern California medical school from 2018-19 were invited to participate in this study via in-person and email announcements. Exclusionary criteria included chronic medical conditions related to inflammation (i.e. asthma, arthritis, cardiovascular disease, cancer), or related to cortisol production (i.e. Cushing's syndrome or Addison's disease), current illness (i.e. upper respiratory infection), periodontitis, oral sores or injuries, use of anti-inflammatory or corticosteroid medications, and pregnancy. After completing informed consent procedures, participants were asked to complete an in-person survey containing sociodemographic questions and validated measures of depression and suicidality. Participants also completed two consecutive days of passive drool saliva collection at home. Samples were

collected at waking, 30 minutes after awakening, noon, and bedtime (referred to here as evening) over two days. All samples were assayed for cortisol, but only the waking and evening samples on day 1 were assayed for CRP. Participants received verbal and written saliva collection guidelines and were asked to record sample collection times and any medications taken on the day of collection. Participants were asked not to eat, drink, or brush their teeth prior to collection, to collect on two consecutive weekdays if possible, and to follow the storage and transport guidelines. Participants were compensated $50 upon completion in the study. Study participation was voluntary, and all survey responses were anonymized. Study and recruitment procedures and materials were approved by the University's Institutional Review Board prior to recruitment.

Measures

Depression Screen

Responses on the Patient Health Questionnaire-9 (PHQ-9) were used to assess depressive symptom severity in the past two weeks. The PHQ-9 focuses on the nine DSM-IV diagnostic criteria for depressive orders (Kroenke & Spitzer, 2002). The PHQ-9 has good reliability (Cronbach's alpha values range from 0.86-0.89) and has been validated for use in student and general population samples (Kroenke et al., 2001). PHQ-9 scores range from 0-27 with a cut-off score of 10 recommended as a threshold for identifying individuals experiencing major depressive disorder with 88% sensitivity and 88% specificity (Kroenke et al., 2010). Here I refer to this cut-off as a positive depression screen (DS), and I use this as a dichotomous variable in analyses.

Suicidality

Responses on the Suicidal Behaviors Questionnaire-Revised (SBQ-R) were used to assess three indicators of suicidality: suicide ideation (SI) in the previous 12 months, lifetime suicidal thoughts and behaviors, and overall suicide risk based on global scores. The SBQ-R is validated for use in college students and in the general population with good reliability (Cronbach's alpha values ranging from 0.76-0.87). Scores range from 3-18 with a cut-off score of 7 having optimal sensitivity (93%) and specificity (95%) to differentiate between non-suicidal and suicidal individuals (Osman et al., 2001). All three indicators of suicidality were used as dichotomous variables created using established cut-offs (Osman et al., 2001).

Salivary Cortisol

Salivary cortisol was used to measure HPA axis function. Salivary cortisol concentrations are strongly correlated with serum cortisol concentrations (Kirschbaum & Hellhammer, 1994) and salivary cortisol is a validated measure of serum levels (Adam & Kumari, 2009; Hellhammer et al., 2009). Cortisol was assayed from all 8 samples of whole saliva and tested in duplicate using a commercially available enzyme-linked immunoassay (ELISA) kits (Salimetrics CAT# 1611550). The test volume was 25 μL with a range of standards from 0.012 – 3.0 μg/dL, and the assay had a lower limit of detection of 0.007 μg/dL. Samples were assayed following manufacturer instructions (Salimetrics, 2018). The total average inter-assay coefficient of variation (CV) was 6.04% and the average intra-assay CV was 5.99%.

Salivary CRP

Salivary CRP was used to measure inflammatory function. Salivary CRP is moderately-strongly correlated with serum CRP in healthy adults (Ouellet-Morin et al., 2011; Punyadeera et al., 2011) and this correlation has been shown to remain stable over two years in women (Out et

al., 2012). CRP was assayed in duplicate from the waking and evening samples on the first day of at-home saliva collection using a commercially available ELISA kit (Salimetrics CAT# 1906503). The test volume was 100 μL with a range of standards from 12.5 – 800 pg/mL, and the assay had a lower limit of detection of 0.042 pg/mL. Samples were assayed following manufacturer instructions. The total average inter-assay coefficient of variation (CV) was 2.63% and the average intra-assay CV was 7.29%.

Composite Indices of Biomeasures

Concentrations of waking and evening cortisol and CRP were used to create 3 types of composite measures that were used in statistical analyses to represent function in the HPA axis and inflammatory systems.

Cortisol/CRP ratio (CORT/CRP): This ratio was created to assess coordination between the HPA axis and inflammatory systems. To assess differences in waking and evening CORT/CRP between mental distress groups (e.g. positive vs negative DS), I created four CORT/CRP categories corresponding to high CORT/high CRP, high CORT/low CRP, low CORT/high CRP, and low CORT/low CRP. I did this using a sex-specific median split of each biomeasure variable (e.g. waking cortisol, waking CRP, evening cortisol, evening CRP) and merging sex-specific groups into one high and one low group per biomeasure. Using these groups, I created two 4-level categorical variables (e.g. waking CORT/CRP and evening CORT/CRP) for the entire sample.

Diurnal slopes of cortisol and CRP: Dynamic functioning in HPA and inflammatory systems across the day were indexed with the slopes from morning to evening levels for each analyte. For cortisol, I calculated the slope by taking the difference between the morning peak

(e.g. 30 minutes after awakening) and the evening (e.g. bedtime) samples and dividing this difference by the time in minutes between the saliva samples (Adam et al., 2017; Pruessner et al., 1997). For CRP, the slope was calculated by taking the difference between the waking sample and the evening sample, and dividing by the time in minutes between saliva samples.

Diurnal output of cortisol and CRP: The average level of HPA and inflammatory system function across the day was indexed using area under the curve with respect to ground (AUCg) composite scores for cortisol and CRP. AUCg was calculated using the summation of trapezoids formula described by Pruessner and colleagues (Jens C. Pruessner et al., 2003).

$$AUCg = \frac{(m_2 + m_1) * t_1}{2} + \frac{(m_3 + m_2) * t_2}{2} + \frac{(m_4 + m_3) * t_3}{2};$$

Where m_1 refers to measurement of cortisol at time 1 (e.g. waking), m_2 refers to measurement of cortisol at time 2 (e.g. 30 minutes after waking), m_3 refers to measurement of cortisol at time 3 (e.g. noon), m_4 refers to measurement of cortisol at time 4 (e.g. evening/bedtime), t_1 refers to minutes between measurement 1 and measurement 2, t_2 refers to minutes between measurement 2 and measurement 3, and), t_3 refers to minutes between measurement 3 and measurement 4 (Jens C. Pruessner et al., 2003). The same formula was adapted for AUCg of CRP, but using only two measurement timepoints (e.g. waking and evening/bedtime).

Covariates

In adjusted models, I controlled for variables that are associated with CRP (and salivary biomeasures in general) in the literature. These included sex (Lakoski et al., 2006; Vetter et al., 2013), age, body mass index (BMI), oral health (e.g. bleeding gums during teeth brushing as a measure of gingival health), use of anti-inflammatory medication (e.g. ibuprofen and/or naproxen), and type of day (e.g. weekday saliva collection or weekend day saliva collection)

(Granger & Taylor, 2020; Lakoski et al., 2006; Out et al., 2012; Vetter et al., 2013). These characteristics were all self-reported. The effect of day type on CRP has not been explored in the literature, but waking cortisol is higher on weekdays which is thought to be due to anticipatory stress (Schlotz et al., 2004). Because cortisol and CRP concentrations effect each other, I assume that the effect of day extends to CRP so I control for it here.

Statistical Analysis

Research question 1

Preliminary analyses included characterizing differences in waking and evening CRP and CRP diurnal slope by sex and mental distress indicators (e.g. positive vs negative DS) using Mann-Whitney mean rank test. I used non-parametric analyses because CRP values were positively skewed and cell sizes were small (waking CRP had a skew of 2.67 and a kurtosis of 9.64, evening CRP had a skew of 4.08 and a kurtosis of 22.7, and CRP diurnal slope had a skew of -2.76 and a kurtosis of 10.3).

I then used separate logistic regression models with each mental distress indicator (i.e., DS, SI, suicide risk, and history of suicidality) as the outcome variable with each main predictor of either: 1) waking CRP concentration; 2) evening CRP concentration; or 3) diurnal slope of CRP. I first assessed bivariate associations between each mental distress indicator and CRP predictor, and, if the overall model and the CRP coefficient were significant ($p < 0.05$), I then controlled for covariates. If the CRP coefficient remained significant ($p < 0.05$) in the full model, covariates were removed and then sequentially added back into the model to ensure that the significant result was not due to overcontrolling. All logistic regression models were run in the entire sample and not separated by sex due to sample size concerns.

Research question 2

To address research question 2a, Fisher's exact test was used to determine differences in mental distress indicators by waking and evening CORT/CRP categories by sex. I stratified by sex in these analyses because Fisher's exact test has lower sample size requirements (Winters et al., 2010).

To address research questions 2b and 2c, I used separate logistic regression models with each mental distress indicator (i.e., DS, SI, suicide risk, and history of suicidality) as the outcome variable and each main predictor of either 1) the interaction term between diurnal CRP and diurnal cortisol slopes, or 2) the interaction term between total diurnal CRP output and total diurnal cortisol output (AUCg). If bivariate associations were significant ($p < 0.05$), I then controlled for all covariates.

Logistic regression model building was conceptually driven, and best model fit was confirmed through likelihood-ratio tests and information criteria. Model robustness was verified through postestimation analyses examining multicollinearity of independent variables, goodness of fit, and area under ROC curve. Postestimation analysis also included examining standardized residuals, leverage, and influence to ensure that individual observations were not driving the models. Statistical analyses were performed using Stata/SE 15.1.

Results

Table 1. Sample Characteristics		
		n (%)
Sex	Male	43 (48.31)
	Female	46 (51.69)
Age (years) [a]	22-24	38 (42.69)
	25-27	41 (46.06)
	28-30	8 (8.98)
	31-33	1 (1.12)
	34-37	1 (1.12)
Race	Asian	42 (47.19)
	White	39 (43.82)
	Other/Prefer not to answer	8 (8.99)
Hispanic/Latino origin	Yes	15 (17.44)
	No	71 (82.56)
Depression screen (DS)	Positive	17 (19.10)
	Negative	72 (80.90)
SI in the previous 12 months	Yes	18 (20.22)
	No	71 (79.78)
Suicide risk screen	Positive	11 (12.36)
	Negative	78 (87.64)
History of suicidality	Yes	33 (37.08)
	No	56 (62.92)
Body Mass Index (BMI) [a]	Normal	64 (71.91)
	Overweight	21 (23.60)
	Obese	4 (4.49)
Bleeding gums [b]	Yes	14 (15.73)
	No	75 (84.27)
Ibuprofen or naproxen use [c]	Yes	41 (46.07)
	No	48 (53.93)

[a] Age and BMI were used as a continuous variables in analyses.

[b] Participants were asked if their gums bleed when brushing teeth.

[c] Those who responded "yes" take ibuprofen or naproxen weekly as needed.

Among those with a positive DS, 7 were male, and 10 were female. Among those with SI, 12 were male and 6 were female. Among those with a positive suicide risk score, 7 were male and 4 were female. And among those with a history of suicidality, 18 were male and 16 were female.

Table 2. Descriptive Statistics of CRP and Cortisol						
CRP (pg/mL)	n	Mean	Median	SD	Min	Max
Waking	89	4082.525	1099.260	7267.419	21.571	32000
Evening	89	798.491	254.770	1496.035	11.028	10012.830
Diurnal Slope	89	-3.5301	-0.5014	6.9350	-33.0057	0.8916
AUCg	89	2286960	717093.7	3833136	42501.09	1.89E+07
Cortisol (μg/dL)						
Waking	89	0.3310	0.2910	0.1740	0.0410	0.8810
Evening	89	0.1270	0.0840	0.2010	0.0040	1.3660
Diurnal Slope	89	-0.00042	-0.00040	0.00035	-0.00154	0.00133
AUCg	89	211.009	180.370	163.118	40.462	1405.440

Preliminary Analyses

Saliva samples were returned by 109 (81.3%) of the 134 medical students that enrolled in the study, which corresponds to 218 total saliva samples assayed for CRP and cortisol (see Table 2 for descriptives). There were no significant differences in demographic characteristics (including year in medical school) or mental distress indicators between those who returned saliva samples and those who did not.

Quality Control and Missingness of Saliva Samples

If samples had CRP concentrations with a coefficient of variation (CV) >15% *and* an absolute difference between duplicates <80 pg/mL, they were retested in duplicate (Salimetrics, 2019). If the retest maintained a CV >15%, they were changed to missing due to unreliability of the CRP estimate. Eight samples were retested due to CV >15%. The retests all had CV <15% and were kept in the dataset. Six CRP samples had concentrations that were above the upper limit of sensitivity (ULOS) of the assay. Four of these values were changed to missing because they remained ULOS and maintained a CV >15% even upon retesting at a higher diluting factor

(1:40), suggesting interference in the assay result. The remaining 2 ULOS samples were replaced with the upper limit of detection of the assay (assuming a 1:40 dilution; 32000 pg/mL) because they each had CVs <1%.

If samples had cortisol concentrations with a CV >15% *and* an absolute difference between duplicates <0.030 μg/dL, they were retested in duplicate (Salimetrics, 2018). If the retest maintained a CV >15%, they were changed to missing. Three samples (1.37% (3/218)) were changed to missing using these criteria. No samples had cortisol concentrations that were above or below the limits of detection of the assay.

I classified extreme values as being ≥4 standard deviations above the mean. I identified 2 cortisol and 4 CRP extreme values but retained these concentrations in the analytic data set as all analyte levels in the study sample were biologically plausible and quality control procedures (detailed above) protected against measurement error in these determinations. Due to equipment failure, 40 (18.3%) samples thawed and were excluded from analyses due to the thaw sensitivity of CRP (Salimetrics, 2019). The total sample size used in analyses was 89 medical students, corresponding to 178 samples of CRP and 178 samples of cortisol.

Table 3a. Relationship Between Waking CRP, Depression Screen, Suicidal Ideation, Suicide Risk, and History of Suicidality

Depression Screen	**Bivariate Model** [a]									
	OR	**SE**	**p**	**95% CI**						
β_1 Waking CRP	1.00006	0.000032	0.045	1.000002	1.00013					
Pseudo R^2	0.0448									
Model significance	0.0485									
Suicidal Ideation	**Bivariate Model** [b]					**Full Covariate Model**				
	OR	**SE**	**p**	**95% CI**		**OR**	**SE**	**p**	**95% CI**	
β_1 Waking CRP	1.00011	0.00004	0.010	1.000027	1.000199	1.00013	4.86E-05	0.005	1.000040	1.00023
β_2 Female						0.266	0.184	0.055	0.069	1.030
β_3 Age						0.798	0.143	0.884	0.733	1.305
β_4 BMI						0.965	0.183	0.759	0.773	1.205
β_5 Bleeding gums						1.683	1.311	0.504	0.365	7.753
β_6 ibuprofen/naproxen						0.933	0.570	0.910	0.281	3.090
Pseudo R^2	0.0888					0.142				
Model significance	0.005					0.0498				
AIC	84.828					85.683				
BIC	89.76					105.224				
Suicide Risk	**Bivariate Model**									
	OR	**SE**	**p**	**95% CI**						
β_1 Waking CRP	0.9996	0.00032	0.214	0.9990	1.00023					
Pseudo R^2	0.0712									
Model significance	0.0432									
History of Suicidality	**Bivariate Model**									
	OR	**SE**	**p**	**95% CI**						
β_1 Waking CRP	1.000078	0.000042	0.063	0.999996	1.000160					
Pseudo R^2	0.0352									
Model significance	0.0437									

[a] Sensitivity analyses revealed that one observation was likely driving the model. When this observation was dropped, waking CRP was no longer significant (p=0.158).

[b] Sensitivity analyses revealed two influential observations. These were dropped from the model because significance of waking CRP and the overall model improved. Total n for this model is 87. Waking CRP remained significant throughout the stepwise addition of covariates. Day type was not included because model significance decreased (p=0.08) and the day type covariate was not significant (p = 0.703) and did not improve AIC/BIC. Waking CRP was significant (p = 0.014) even when day type was included in the model.

Table 3b. Relationship Between Diurnal CRP Slope, Depression Screen, Suicidal Ideation, Suicide Risk, and History of Suicidality

Depression Screen	**Bivariate Model**					**Full Covariate Model** [a]				
	OR	**SE**	**p**	**95% CI**		**OR**	**SE**	**p**	**95% CI**	
β_1 CRP slope	0.934	0.031	0.039	0.875	0.997	0.918	0.035	0.026	0.851	0.990
β_2 Female						1.356	0.853	0.629	0.395	4.656
β_3 Age						1.150	0.150	0.284	0.890	1.486
β_4 BMI						1.074	0.113	0.499	0.874	1.319
β_5 Bleeding gums						3.292	2.376	0.099	0.800	13.549
β_6 ibuprofen/naproxen						0.775	0.483	0.683	0.229	2.629
β_7 Weekend day						0.959	0.791	0.960	0.190	4.832
Pseudo R^2	0.0482					0.1295				
Model significance	0.0408					0.133				
AIC	86.62					90.820				
BIC	91.60					110.540				
*Suicidal Ideation**	**Bivariate Model**									
	OR	**SE**	**p**	**95% CI**						
β_1 CRP slope	0.941	0.031	0.065	0.882	1.004					
Pseudo R^2	0.0369									
Model significance	0.069									
Suicide Risk	**Bivariate Model**									
	OR	**SE**	**p**	**95% CI**						
β_1 CRP slope	1.060	0.079	0.431	0.917	1.226					
Pseudo R^2	0.0131									
Model significance	0.3508									
History of Suicidality	**Bivariate Model**									
	OR	**SE**	**p**	**95% CI**						
β_1 CRP slope	0.965	0.030	0.262	0.908	1.027					
Pseudo R^2	0.0109									
Model significance	0.2581									

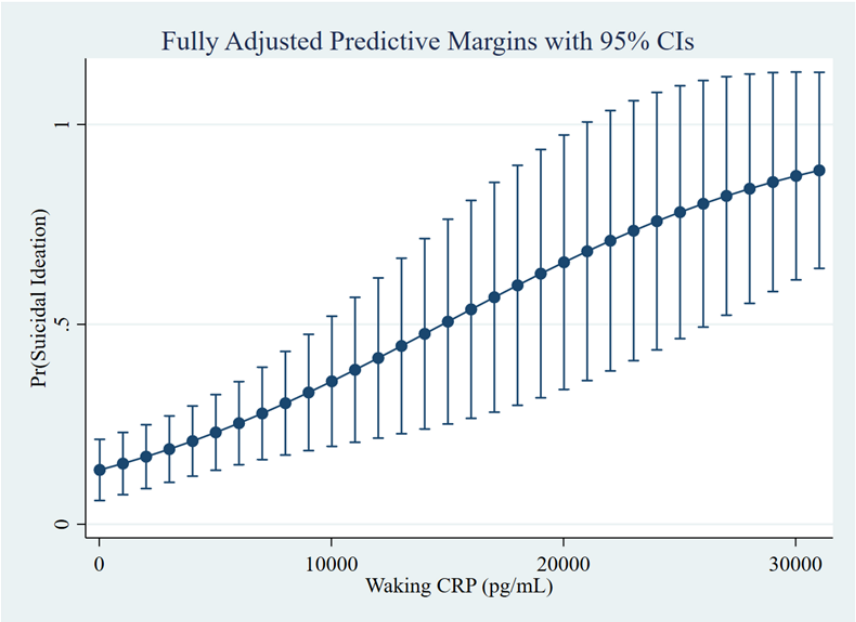
[a] Sensitivity analyses revealed 3 influential observations that were likely driving the association between diurnal CRP slope and DS. Once dropped, waking CRP was no longer significant (p=0.144).

Associations between waking CRP concentrations and mental distress indicators – Research question 1

In logistic regression, waking CRP was positively associated with DS but sensitivity analyses revealed that one observation was likely driving the association (see Table 3a for additional details). This observation had the third highest waking CRP and third highest continuous depression score (15). Waking CRP was also associated with SI in the unadjuated logistic regression as well as after the stepwise addition of covariates (Table 3a). The probability of having SI increased from 13.5% (95% CI: 0.05 – 0.21), at the lowest waking CRP in this sample (21.5 pg/mL) to 88.5% at the highest waking CRP in this sample (32,000 pg/mL; 95% CI: 0.63 – 1.13) (Figure 1). The probability of having SI was approximately 20.7% (95% CI: 0.12 – 0.29) for the mean waking CRP concentration in this study sample (4,082.5 pg/mL) Suicide risk and history of suicidality were not associated with waking CRP.

In preliminary analyses stratified by sex, waking CRP was significantly associated with a positive DS in males (Figure 2a).

Figure 2. Predicted probabilities of SI by waking CRP concentration



The range of waking CRP concentrations plotted here corresponds to the range of waking CRP concentrations in this sample, 21.5 pg/mL to 32,000 pg/mL. In this model, SI is the outcome variable and waking CRP is the main independent variable.

Associations between evening CRP concentrations and mental distress indicators – Research question 2

In preliminary analyses stratified by sex, evening CRP was significantly positively associated with a positive DS in males (Figure 2a), SI in males (Figure 2b), and suicide risk in females (Figure 2c).

In logistic regression analyses of the full study sample, evening CRP was not associated with any mental distress indicator (Appendix B).

Associations between diurnal CRP slope and mental distress indicators – Research question 3

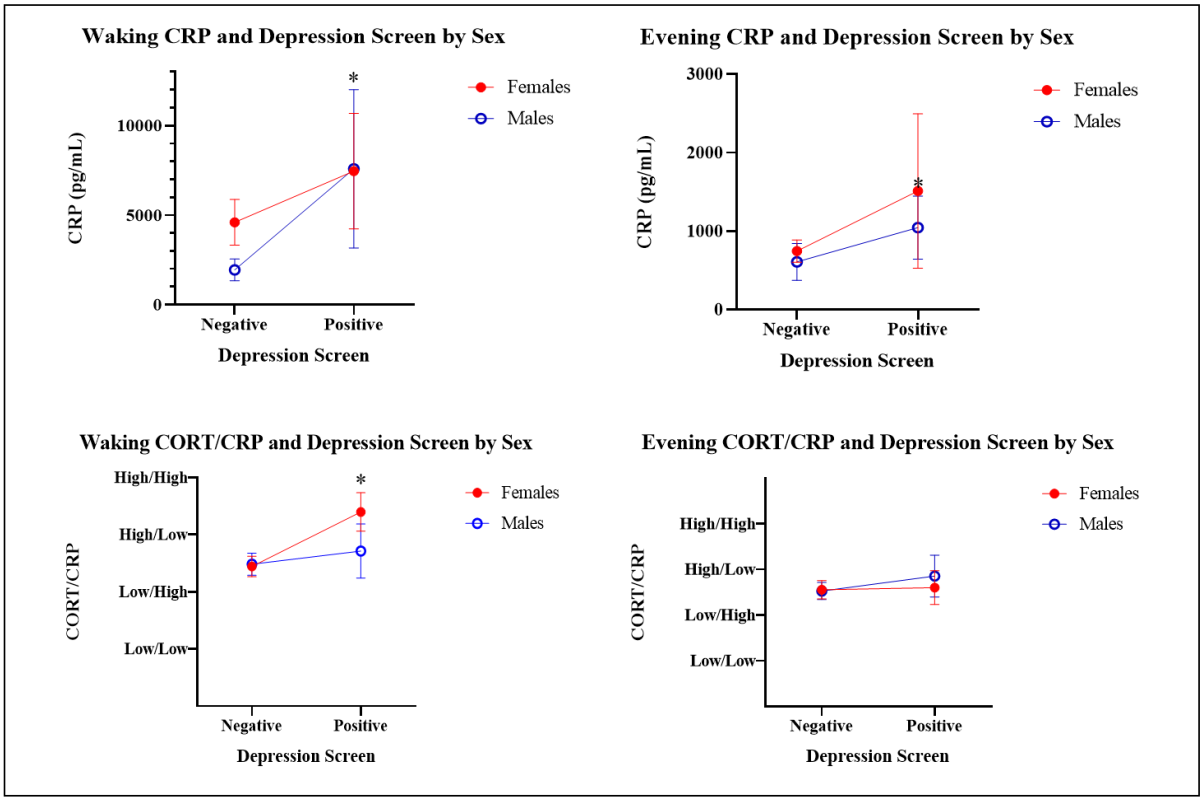
In preliminary analyses stratified by sex, the average diurnal CRP slope for males with a positive DS was significantly steeper ($m = -7.22$, $p < 0.05$) than the average diurnal slope of males with a negative DS ($m = -1.44$). The average diurnal CRP slope for females with a positive

DS (m = -6.72, $p < 0.05$) was also significantly steeper than the average diurnal slope of females with a negative DS (m = -4.01).

In logistic regression analyses conducted using the full study sample, the diurnal CRP slope was associated with DS, but sensitivity analyses revealed that three observations were likely driving the significant association (see Table 3c for additional details). These three observations had the three most negative diurnal CRP slopes in the dataset. Two of these also had a positive DS.

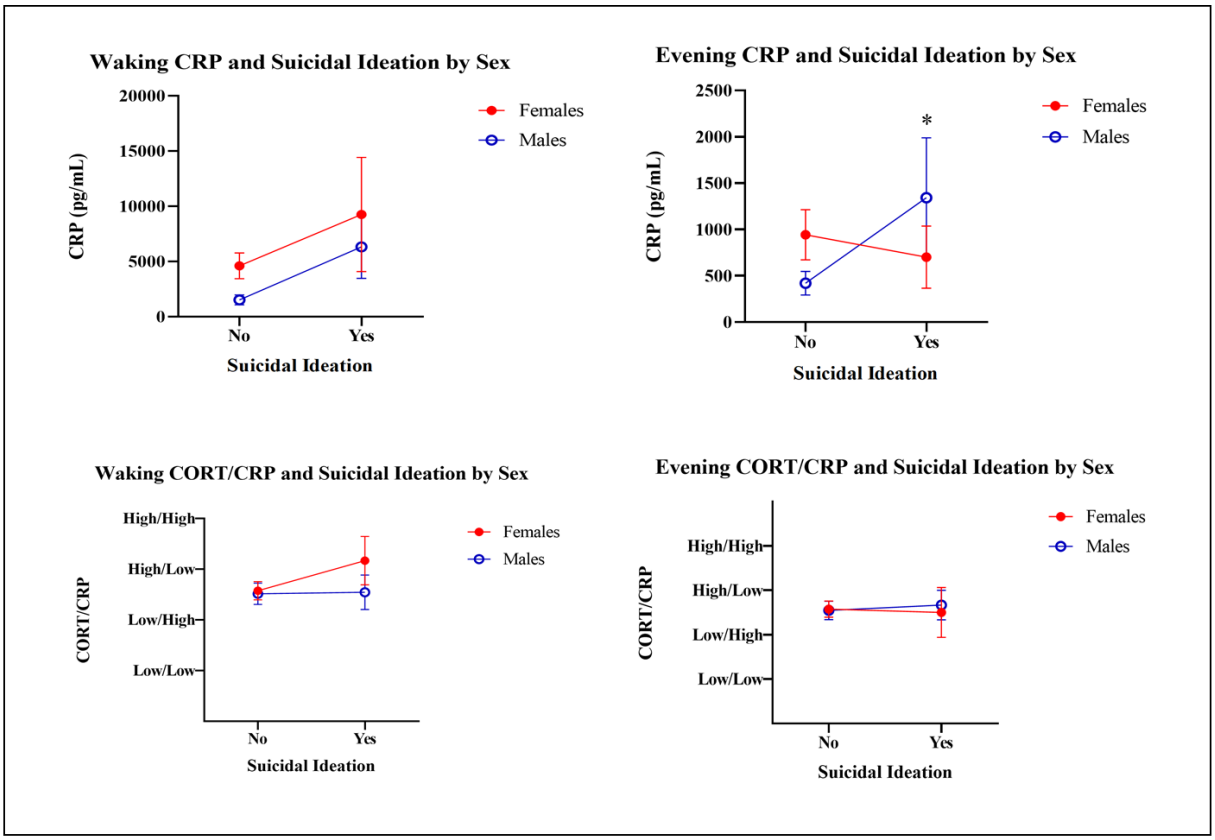
SI, suicide risk, and history of suicidality were not associated with diurnal CRP slope.

Figure 2a. Mean waking and evening CRP and CORT/CRP by DS and Sex



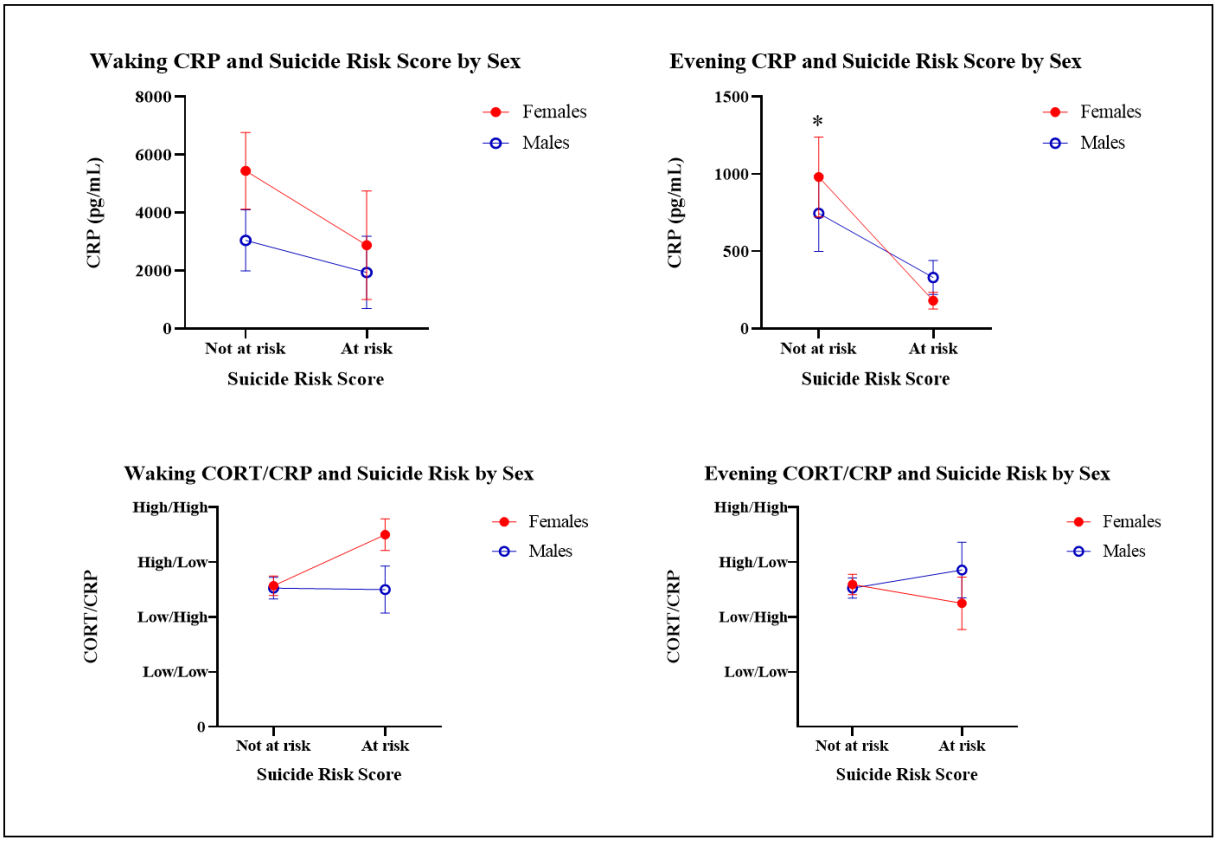
Bivariate associations between waking and evening CRP and DS were analyzed with Mann-Whitney mean rank test and bivariate associations between waking and evening CORT/CRP and DS were analyzed with Fisher's exact test. Waking and evening CRP were significantly higher in males with a positive DS ($p < 0.05$) relative to males with a negative DS. Females with a positive DS were more likely ($p < 0.05$) to fall into the High/High group relative to females with a negative DS.
Error bars indicate standard error of the mean.
* $p < 0.05$

Figure 2b. Mean waking and evening CRP and CORT/CRP by SI and Sex



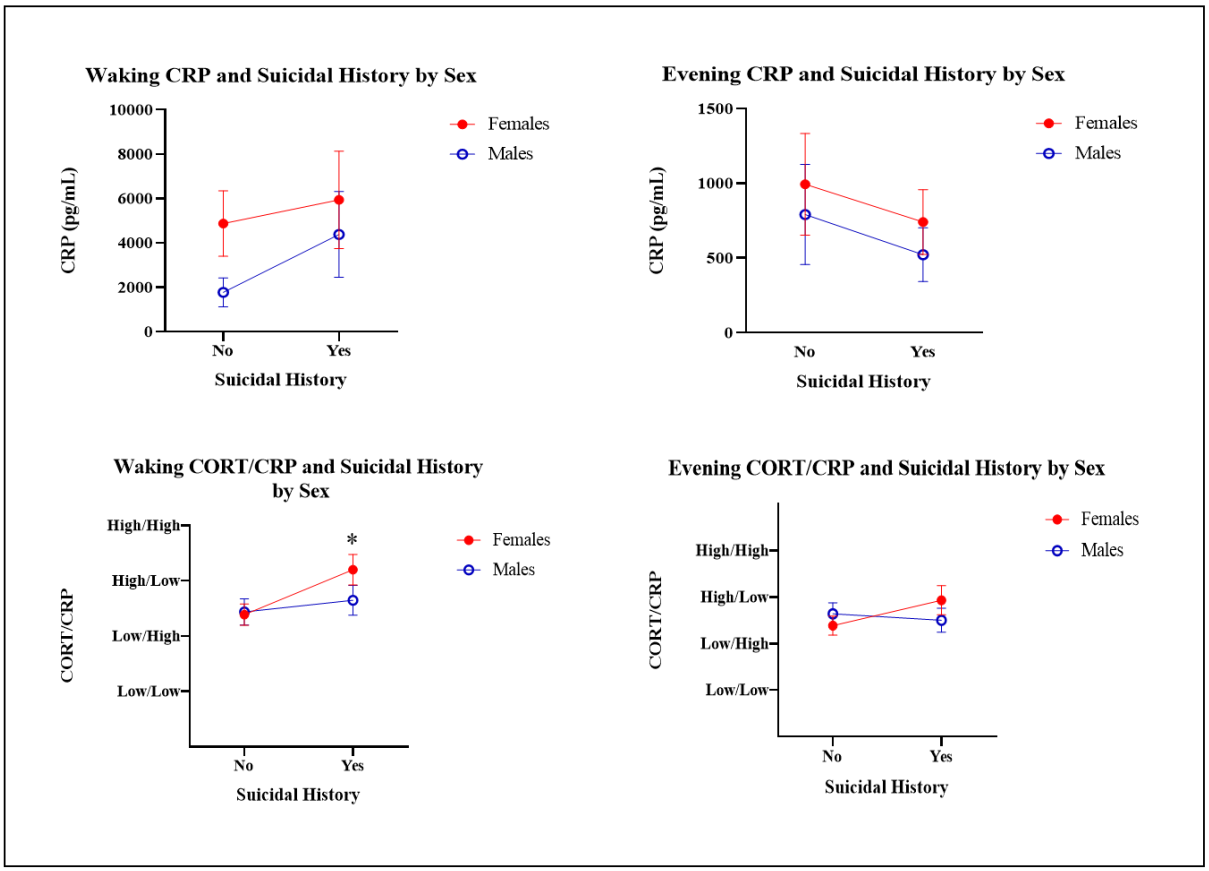
Bivariate associations between waking and evening CRP and SI were analyzed with Mann-Whitney mean rank test and bivariate associations between waking and evening CORT/CRP and SI were analyzed with Fisher's exact test. Evening CRP was significantly higher ($p < 0.05$) in males with SI relative to males without SI. There were no other significant differences.
Error bars indicate standard error of the mean.
* $p < 0.05$

Figure 2c. Mean waking and evening CRP and CORT/CRP by Suicide Risk and Sex



Bivariate associations between waking and evening CRP and suicide risk were analyzed with Mann-Whitney mean rank test and bivariate associations between waking and evening CORT/CRP and suicide risk were analyzed with Fisher's exact test. Evening CRP was significantly lower ($p < 0.01$) in females with positive suicide risk score relative to females with a negative suicide risk score. There were no other significant differences.
Error bars indicate standard error of the mean.
* $p < 0.05$

Figure 2d. Mean waking and evening CRP and CORT/CRP by History of Suicidality and Sex



Bivariate associations between waking and evening CRP and history of suicidality were analyzed with Mann-Whitney mean rank test and bivariate associations between waking and evening CORT/CRP and history of suicidality were analyzed with Fisher's exact test. Females with a history of suicidality were more likely ($p = 0.055$) to fall into the High/High group relative to females without a history of suicidality. There were no other significant differences. Error bars indicate standard error of the mean.
* $p < 0.05$

Associations between CORT/CRP and mental distress indicators – Research question 2a

Females with a positive DS were significantly more likely ($p < 0.05$) to fall into the high waking CORT/CRP group relative to females with a negative DS (Figure 2a). Females with a history of suicidality were significantly more likely ($p < 0.05$) to fall into the high waking CORT/CRP group relative to females without a history of suicidality (Figure 2d). There were no significant differences in waking CORT/CRP between males for any mental distress indicator. There were no significant differences in waking CORT/CRP between females with and without

SI and with and without a positive suicide risk score (Figures 2a-2d). There were no significant differences in evening CORT/CRP for males or females by any mental distress group.

Associations between the interaction of cortisol diurnal slopes and CRP diurnal slopes and mental distress indicators – Research question 2b

There were no significant associations between the interaction of diurnal cortisol and CRP slopes and indicators of mental distress.

Associations between the interaction of cortisol AUCg and CRP AUCg and mental distress indicators – Research question 2c

There were no significant associations between the interaction of cortisol AUCg and CRP AUCg and indicators of mental distress.

Discussion

Summary of findings

I present results from a series of analyses exploring relations between inflammatory and NEI activity and mental distress among a sample of moderately healthy, young medical students. These findings are preliminary due to the small sample size and the exploratory nature of these analyses. However, my findings are novel and provide several areas of investigation for future researchers interested in the biopsychosocial pathways underlying depression and suicidality as well as translational researchers interested in developing new tools for designing and evaluating prevention and intervention efforts.

Regarding relations between CRP and mental distress, I found: a) higher waking CRP was associated with SI in the full sample; and b) while waking and evening levels of CRP were not associated with DS, suicide risk, or history of suicidality in the full study sample; there were sex-specific associations between c) waking CRP and DS; d) evening CRP, DS, SI, and suicide risk; d) waking CORT/CRP in DS and history of suicidality; and e) diurnal CRP slope and DS. For all significant relations, with the exception of lower evening CRP in females with suicide risk, higher risk of mental distress was seen for participants with higher CRP levels and steeper declines in CRP levels across the day.

In the full sample, higher waking CRP concentrations were associated with SI even after controlling for covariates. This is the first study to find associations between SI and CRP assayed from saliva collected at home in a non-clinical sample of moderately healthy young adults. This finding is in accordance with findings from other studies. To the best of my knowledge, there has only been one other study to assess associations between CRP and SI in a non-clinical sample. The association between higher serum CRP and SI in the previous 12 months has also been observed in a large (n=4693) study of adults ages 20-81 in the Korean general population (Park & Kim, 2017). Additional support for these findings comes from studies of psychiatric inpatients and outpatients which highlights a potential difference in severity of symptoms. In psychiatric inpatients, serum CRP was higher among those with SI relative to controls (Gibbs et al., 2016). In depressed psychiatric out-patients, current SI was associated with higher serum CRP (relative to patients with past SI), even after controlling for depressive symptoms (C. C. Chang et al., 2017). Similarly, a higher inflammatory index (including CRP concentrations) in serum was associated with high SI in depressed inpatients relative to patients with low SI and controls (O'Donovan et al., 2013). There have also been studies with null findings. There was no

association between serum CRP and SI in two samples of depressed psychiatric inpatients (Cáceda et al., 2018; Courtet et al., 2015). Every individual in these samples had severe depression, so it is possible that inflammatory processes due to severe depression have confounded the association between CRP and SI in these studies, despite efforts to control for depression (Valkanova et al., 2013). Each of the above studies had a cross-sectional design, meaning that the data cannot speak to the temporality of the association between increased inflammation and SI. Longitudinal studies with multiple sample collection waves are needed to address this gap in knowledge.

Higher waking CRP concentration and flatter diurnal CRP slope was also associated with a positive DS before controlling for demographic and health covariates, but not when excluding influential cases with especially high CRP concentrations relative to the study sample. These influential observations were also from participants with positive DS and between one and three indices of suicidality (e.g. SI, positive suicide risk, and history of suicidality). These cases may represent an important part of the medical student community that were not sampled at a high enough proportion to truly investigate, but is worthy of additional research. This trend should be investigated in future studies with a sufficient sample size to assess differences in risk profiles, which may elucidate intervention needs.

In the total sample, waking and evening CRP concentrations were not associated with DS, suicide risk, or history of suicidality. These nonsignificant findings may be due in part to the young and moderately healthy nature of the sample. Although this has not been explored in the literature in the context of suicidality, there is evidence that a high inflammatory state is not present in the early stages of depression (Cubała & Landowski, 2014) . Additionally, participants in this study were able to choose the day of at-home saliva collection. While I did not collect

information on perceived stress or mood on the days of saliva collection, I assume that participants chose a relatively low-stress day to collect the samples, avoiding days with high levels of academic and clinical responsibilities. The potential low-stress conditions under which samples were collected could explain some of the nonsignificant findings. It is also possible that associations between inflammatory activity, depression, and suicidality need to be investigated separately by sex given the different inflammatory properties of sex hormones. Estrogens are pro-inflammatory, and are produced in a greater amount in females, and contrastingly, androgens are anti-inflammatory, and are produced in a greater amount in males (Schmidt et al., 2006).

Preliminary analyses, which stratified by sex, showed interesting trends. These findings suggest CRP concentrations may be a more salient predictor of mental distress in males, but this needs to be investigated in a larger sample to ensure adequate power. Higher waking and evening CRP were associated with a positive DS in males, and higher evening CRP was also associated with SI in males. In females, a lower evening CRP was associated with positive suicide risk score. Contrary to my hypothesis, a steeper diurnal CRP slope was associated with a positive DS in both males and females. A steeper slope indicates a high waking CRP concentration that drops considerably by evening. High waking inflammatory activity is associated with poor sleep quality and inadequate sleep (Huang et al., 2017), and as we know from Chapter 1, this sample has a high prevalence of poor sleep quality. This could explain the high waking inflammatory activity.

Preliminary analyses also suggested that waking CORT/CRP concentrations may be more important markers of risk in females. A high CORT/CRP waking state was associated with a positive DS and history of suicidality in females. This is in contrast to the findings by Suarez and colleagues that females with higher depressive symptoms showed a low CORT/high CRP state

(Suarez et al., 2015). This difference in cortisol concentration could be due to the fact that Suarez and colleagues assayed cortisol from plasma that was collected in the laboratory at approximately 9AM, missing the high morning peak of cortisol. Anticipatory stress may also be driving the high waking cortisol state in my findings (Wirtz et al., 2007).

Limitations

These preliminary findings are encouraging although this study has limitations. Due to cross-sectional design and small sample, this study is underpowered to robustly investigate the complex cross-system relations of NEI coordination. Longitudinal research is needed to assess temporal associations between salivary inflammatory markers and mental distress indices. Based on previous studies and my findings, it is important to assess associations between salivary CRP and indicators of mental distress separately by sex. This requires a larger sample size. The small sample also presents statistical limitations in the ability to estimate relations between biomeasures and mental distress given the low prevalences of positive mental distress indicators in the sample. The proportion of participants reporting a positive DS was lower than expected based on the medical student literature. This could be due in part to the fact that more than 1/3 of the sample were in their first year of medical school. Additionally, another limitation is that the survey was not truly anonymized in that the design of the study involved an in-person appointment with one member of the research team. Because mental health is stigmatized in this population, the data may be subject to a social desirability effect. Future studies should aim to make survey collection anonymous to ensure participant comfort. Further, although at-home saliva collection is non-invasive and convenient for the participant, I am relying on the accuracy of the participant's sample collection time diary and on their compliance with sample storage and transport guidelines (i.e. I do not have information about the cold-chain prior to the samples

being returned). Collecting saliva samples in a controlled, laboratory environment would mitigate these issues.

Strengths

Although it has its limitations, at-home saliva collection is also a strength of this study. Participants collected saliva at home which is likely much less stress-inducing than collecting the saliva in a laboratory environment. Even under these low-stress conditions, I observed associations between mental distress and CRP in this sample. Beyond this study, diurnal CRP slope has yet to be considered a salient determinant of depression or suicidality. These findings highlight the need for future studies to expand collection of CRP beyond one baseline timepoint and integrate multisystem measurements to obtain a more holistic picture of the pathophysiology of depression and suicidality. This would facilitate investigation into the association of diurnal CRP activity and disease.

Implications and Conclusions

Future studies should utilize a prospective cohort design and follow medical students through medical school and ideally through residency training to investigate the temporality of increased inflammation, depression, and suicidality. Future studies should also include more than one medical school to increase generalizability of findings with the long-term goal of informing future intervention studies. Although these findings are exploratory and have a small sample size, they demonstrate the feasibility and promise of assessment of NEI regulation in ecologically valid settings among this population. Results are promising and suggest that biomarkers may be a useful tool for identifying risk of depression and suicidality, although much additional work is needed.

CHAPTER 5
CONCLUSION

The purpose of this dissertation was to identify potential biopsychosocial risk factors for depression and suicidality in a sample of young, presumed healthy medical students. This dissertation also describes associations of salivary neuroendocrine-immune biomarkers, cortisol and C-reactive protein (CRP) among the same medical students, to inform research into the development of biomarkers as screening tools for early depressive symptomology and suicidality. Depression was explored through a screen, and the construct of suicidality was broken up into three separate indices (e.g., suicidal ideation in the previous 12 months, overall suicide risk, and history of suicidality) throughout this dissertation to explore three unique dimensions of suicidality. Separate indices were used to assess the extent to which each index was correlated with specific risk factors for the purpose of informing future intervention studies tailored to medical students.

Summary of findings

In Chapter 2, I began this examination through determining the prevalence of depression and indices of suicidality and potential risk factors in this sample. The prevalence of positive depression screens in this sample was lower (16%) than previously reported in literature for medical students, but higher than general population estimates. However, 41% of medical students in this study had at least mild depressive symptomology. The prevalence of suicidal ideation in the previous 12 months was more than double (17%) what has been reported in other samples of medical students. Cumulative suicide risk was relatively low (10.5%) in this sample, compared to the prevalence of suicidal ideation in the previous 12 months. More than one-third

(34%) of the sample had a history of suicidality. There was also a high prevalence of potential risk factors: 94% had at least moderate feelings of impostor syndrome, 59% experienced poor sleep quality in the previous month, 55% had moderate or high levels of perceived stress, 50% had a hazardous drinking screen, 25% had difficulty paying monthly bills, 17% had financial need, and 14% had some level of food insecurity.

The risk factors that were statistically significantly associated with indicators of mental distress included poor sleep quality, high perceived stress, feelings of impostor syndrome, and bill payment difficulty. Positive depression screen was associated with poor sleep quality, high perceived stress, impostor feelings, and bill payment difficulty. Suicidal ideation and suicide risk were only associated with impostor feelings, and history of suicidality was associated with impostor feelings and poor sleep quality. Impostor feelings were statistically significantly associated with each mental distress indicator, even after controlling for depression in suicidality models. These findings suggest the need for future studies to focus on impostor syndrome as a salient target for intervention. Alcohol use, financial need, and food insecurity were not associated with any indicators of mental distress.

In Chapter 3, I evaluated associations between diurnal cortisol activity and indicators of mental distress. Higher diurnal cortisol output was statistically significantly associated with suicide risk after controlling for covariates. Depression screen and suicidal ideation were not associated with diurnal cortisol output. The interaction between mental distress indicators and diurnal slope was not associated with cortisol output. Higher diurnal cortisol output was also found to be associated with a history of suicidality.

In Chapter 4, I examined associations between diurnal CRP activity and indicators of mental distress. To explore neuroendocrine-immune dysregulation, I also examined associations

between the interaction of diurnal cortisol activity and diurnal CRP activity with indicators of mental distress. Preliminary analyses were stratified by sex. Findings included significantly higher waking and evening CRP in males with positive depression screens, higher evening CRP in males with suicidal ideation, and lower evening CRP in females with positive suicide risk scores. History of suicidality was not associated with waking or evening CRP. A steeper decline in diurnal CRP was associated with a positive depression screen in males and females. Diurnal CRP slope was not associated with suicidal ideation, suicide risk, or history of suicidality. A positive depression screen and history of suicidality were associated with a high waking cortisol/CRP ratio in females. Waking ratios of cortisol/CRP were not associated with suicidal ideation or suicide risk. Evening ratios of cortisol/CRP were not associated with any measure of mental distress. In analyses collapsing across sexes, higher waking CRP was associated with suicidal ideation. The interaction between diurnal cortisol activity and diurnal CRP activity (conceptualized using area under the curve with respect to ground (AUCg) and diurnal slope) was not associated with any indicator of mental distress.

Study Implications

These findings have important implications for advancing research, programs, and policy.

Research: This dissertation provides preliminary evidence that HPA and inflammatory activity are disrupted in a sample of young adults with pre-clinical levels of mental distress. This dissertation takes the temporal context of the development of NEI dysregulation into consideration when interpreting the null findings. Specifically, data collection utilized for all chapters occurred in the early stages of medical training (years 1-4 of medical school) where the majority of study participants (79%) were under the age of 27. I expect to see greater prevalence of depression and suicidality related NEI dysregulation as medical students progress through

residency training and into independent practice as physicians. This dissertation provides a baseline assessment of depression, suicidality, and risk factors experienced by medical students early in training. I hypothesize that future longitudinal investigations with this same sample of medical students, and with all survey and biomarker metrics repeated, would reveal more striking prevalence rates of mental distress and NEI disruption in later years. Longitudinal studies are needed to follow students throughout their careers to assess changes in prevalence of mental distress and risk factors for mental distress, which may highlight the need for interventions at specific training and/or career stages. Additionally, all salivary biomarkers were from self-collected samples at home. Often biomarkers collected as part of research studies reflect slightly activated physiological states as they are performed by strangers and/or in laboratory setting. Here, participants in this study collected on their own and at-home, and were able to choose the day of at-home saliva collection. I did not collect information on perceived stress or mood on the days of saliva collection, but I assume that many participants chose a relatively low-stress day to collect the samples in between academic and clinical responsibilities. The potential low-stress and basal conditions under which samples were collected could explain some of the nonsignificant findings. Future research can build upon these findings to address these questions regarding biomarker measurement and study design.

Programs and Policy: First, the findings suggest that there is a high prevalence of factors associated with increased risk for suicide in this sample of medical students, and that sleep quality, perceived stress, feelings of impostor syndrome, and bill payment difficulty may be important targets for future intervention studies in medical students. Impostor syndrome was independently associated with depression screen and all indices of suicidality. The present findings indicate the need for future intervention that includes increasing education about

impostor syndrome and supporting the development of medical students' professional identities through formal institutional programs in order to reduce feelings of impostor syndrome. This has not been explored in medical students, but has been demonstrated as an effective intervention in academic faculty (Hutchins & Rainbolt, 2017).

It is important that medical students learn to recognize depression and suicidal thoughts and behaviors in themselves, and are equipped with tools to work through these issues. While seeking professional help is always advisable in situations of depression and suicidality, the literature has shown over and over that medical students and physicians alike are not comfortable seeking help (Center et al., 2003). This is due, largely in part, to the stigmatization of mental illness in the medical community and the concern that seeking help will jeopardize an individual's reputation, career prospects, and medical board licensure (Center et al., 2003; Rosenthal & Okie, 2005; Schwenk et al., 2010).

These concerns are well founded because approximately two-thirds of states have medical licensure applications that ask questions about mental health that violate the American Disabilities Act (Jones et al., 2018), and would be considered inappropriate on an application for any other type of career. A nationwide study found that 40% of physicians surveyed said that these questions act as an indirect barrier to seeking help for what would otherwise be considered treatable mental health issues, as a "yes" answer leads to the demand for all medical records (Dyrbye et al., 2017; Jones et al., 2018). The current state of licensure questions also go against the American Psychiatric Association's position that information about past mental health treatment is not a salient predictor of current impairment and current ability to practice medicine, and that these questions are therefore needlessly discriminatory (Walker, 2004).

Compounding the issue, medical students and physicians who are depressed are more likely than their non-depressed peers to hold stigmatized attitudes toward depression (Schwenk et al., 2010, 2008). Given the difficulty in changing field-wide attitudes and beliefs, it is important to equip future physicians with self-help tools so that while we are waiting for grander societal shifts in mental illness stigma, we can begin to address the problem at the individual level. To this end, as was the focus of this dissertation research, future intervention studies in medical students should target risk factors that are realistically modifiable during the course of medical training. This rationale is what makes finding a reliable biomarker that reflects risk for mental distress particularly important in this population that errs on the side of not reporting symptoms at any stage of their training or career.

The current coronavirus pandemic has also highlighted the urgent need to support medical student and physician mental health. Prior the pandemic, physicians were already experiencing "unprecedented levels of burnout and poor mental health", and the pandemic has exacerbated these issues by increasing exposure to dying patients and therefore increasing guilt and impostor feelings, increasing social isolation among physicians who are on the front-lines due to mandatory social distancing from their families, and public pushback on public health policies (i.e. social distancing and mask wearing) to "flatten the curve" of coronavirus infections (Abbasi, 2020). The need to prioritize the mental health of medical students and physicians has possibly never been greater.

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APPENDIX A
Chapter 3 Supplemental Tables

Supplemental Table 1. Maximum likelihood estimates for daily cortisol output and depression screen data (log-transformed)

	Base model				Spline covariate model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive PHQ9]	0.21590	0.051	-0.00123	0.43303	0.21166	0.061	-0.00968	0.43300
β2 [Sampletimepre30]	-	-	-	-	0.00307	0.090	-0.00048	0.00663
β3 [Sampletimepost30]	-	-	-	-	-0.00252	0.000	-0.00270	-0.00234
β4 [Female]	-	-	-	-	-	-	-	-
β5 [Daytype]	-	-	-	-	-	-	-	-
β6 [Bleeding gums while brushing]	-	-	-	-	-	-	-	-
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-	-	-	-
log-likelihood	-1168.31				-867.09			
AIC	2346.61				1748.18			
BIC	2370.40				1781.49			
ICC| person level	0.0991		0.0560	0.1696	0.2978		0.2265	0.3806
ICC| sample day level	0.0991		0.0560	0.1696	0.2978		0.2265	0.3806

	Spline slope model				Full model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive PHQ9]	0.17413	0.108	-0.03827	0.38653	0.1212	0.2620	-0.0907	0.3331
β2 [Sampletimepre30]	0.00354	0.044	0.00010	0.00699	0.0037	0.0380	0.0002	0.0072
β3 [Sampletimepost30]	-0.00257	0.000	-0.00281	-0.00234	-0.0026	0.0000	-0.0028	-0.0023
β4 [Female]	-	-	-	-	0.1936	0.0230	0.0273	0.3598
β5 [Daytype]	-	-	-	-	-0.0667	0.3170	-0.1974	0.0639
β6 [Bleeding gums while brushing]	-	-	-	-	0.1977	0.0880	-0.0296	0.4250
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-0.1207	0.1550	-0.2868	0.0455
log-likelihood	-843.36				-821.55			
AIC	1710.72				1675.10			

BIC	1767.82			1750.93			
ICC| person level	0.2910	0.1775	0.4385	0.2918	0.1768	0.4414	
ICC| sample day level	0.2910	0.1775	0.4385	0.2918	0.1768	0.4414	

Supplemental Table 2. Maximum likelihood estimates for daily cortisol output and suicide ideation data (log-transformed)

	Base model				Spline covariate model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive SI]	0.09624	0.351	-0.10603	0.29851	0.08148	0.439	-0.12486	0.28782
β2 [Sampletimepre30]	-	-	-	-	0.00308	0.089	-0.00047	0.00663
β3 [Sampletimepost30]	-	-	-	-	-0.00252	0.000	-0.00270	-0.00234
β4 [Female]	-	-	-	-	-	-	-	-
β5 [Daytype]	-	-	-	-	-	-	-	-
β6 [Bleeding gums while brushing]	-	-	-	-	-	-	-	-
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-	-	-	-
log-likelihood	-1150.76				-831.97			
AIC	2311.53				1677.93			
BIC	2335.28				1711.18			
ICC| person level	0.0799		0.0405	0.1515	0.3055		0.2335	0.3886
ICC| sample day level	0.0799		0.0405	0.1515	0.3055		0.2335	0.3886

	Spline slope model				Full model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive SI]	0.082167	0.426	-0.11999	0.284323	0.1147	0.278	-0.0926	0.3221
β2 [Sampletimepre30]	0.003543	0.044	-0.00281	-0.00234	0.0037	0.038	0.0002	0.0072
β3 [Sampletimepost30]	-0.00257	0.000	-1.33145	-1.12131	-0.0026	0.000	-0.0028	-0.0023
β4 [Female]	-	-	-	-	0.2144	0.012	0.0472	0.3816
β5 [Daytype]	-	-	-	-	-0.0740	0.268	-0.2048	0.0568
β6 [Bleeding gums while brushing]	-	-	-	-	0.2216	0.054	-0.0038	0.4471
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-0.1225	0.149	-0.2890	0.0440

log-likelihood	-815.71			-793.41		
AIC	1655.42			1618.81		
BIC	1712.42			1694.51		
ICC| person level	0.3008	0.1870	0.4459	0.2989	0.1839	0.4381
ICC| sample day level	0.3008	0.1870	0.4459	0.2989	0.1839	0.4381

Supplemental Table 3. Maximum likelihood estimates for daily cortisol output and history of suicidality data (log-transformed)

	Base model				Spline covariate model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive Life History]	0.13086	0.115	-0.03201	0.29032	0.14097	0.095	-0.02476	0.30669
β2 [Sampletimepre30]	-	-	-	-	0.00310	0.122	-0.00045	0.00666
β3 [Sampletimepost30]	-	-	-	-	-0.00252	0.000	-0.00270	-0.00234
β4 [Female]	-	-	-	-	-	-	-	-
β5 [Daytype]	-	-	-	-	-	-	-	-
β6 [Bleeding gums while brushing]	-	-	-	-	-	-	-	-
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-	-	-	-
log-likelihood	-1149.97				-830.89			
AIC	2309.95				1675.79			
BIC	2333.70				1709.04			
ICC| person level	0.1023		0.0584	0.1731	0.3018		0.2300	0.3847
ICC| sample day level	0.1023		0.0584	0.1731	0.3018		0.2300	0.3847
	Spline slope model				Full model			
	Est	p	95% CI		Est	p	95% CI	
Fixed effects								
β1 [Positive Life History]	0.13882	0.094	-0.02361	0.30124	0.15266	0.063	-0.00822	0.31354
β2 [Sampletimepre30]	0.00357	0.066	-0.00021	0.00655	0.00372	0.057	-0.00010	0.00675
β3 [Sampletimepost30]	-0.00257	0.000	-0.00281	-0.00234	-0.00258	0.000	-0.00282	-0.00235

β4 [Female]	-	-	-	-	0.21675	0.010	0.05171	0.38180
β5 [Daytype]	-	-	-	-	-0.07523	0.259	-0.20579	0.05533
β6 [Bleeding gums while brushing]	-	-	-	-	0.20779	0.069	-0.01595	0.43152
β7 [Use of ibuprofen/naproxen]	-	-	-	-	-0.12995	0.123	-0.29515	0.03526
log-likelihood	-814.69				-792.35			
AIC	1653.37				1616.69			
BIC	1710.37				1692.39			
ICC| person level	0.2910		0.1774	0.4385	0.2882		0.1631	0.4309
ICC| sample day level	0.2910		0.1774	0.4385	0.2882		0.1631	0.4309

Supplemental Table 4. Interaction of the slope of the morning rise of cortisol and depression screen (log-transformed)

	Full model with morning rise slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive PHQ9]	0.04659	0.725	-0.21320	0.30637
β2 [Sampletimepre30]	0.00293	0.132	-0.00088	0.00674
β3 [Sampletimepre30##Positive PHQ9]	0.00424	0.331	-0.00431	0.01278
β4 [Sampletimepost30]	-0.00258	0.000	-0.00282	-0.00234
β5 [Female]	0.19371	0.022	0.02745	0.35996
β6 [Daytype]	-0.06684	0.316	-0.19749	0.06381
β7 [Bleeding gums while brushing]	0.19749	0.089	-0.02980	0.42478
β8 [Use of ibuprofen/naproxen]	-0.12068	0.155	-0.28683	0.04547
log-likelihood	-821.0858			
AIC	1676.172			
BIC	1756.74			
ICC| person level	0.29005		0.17529	0.43985
ICC| sample day level	0.29005		0.17529	0.43985

Supplemental Table 5. Interaction of the slope of the daily fall of cortisol and depression screen (log-transformed)

	Full model with daily fall slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive PHQ9]	0.08333	0.460	-0.13758	0.30424
β2 [Sampletimepre30]	0.00370	0.037	0.00021	0.00718
β3 [Sampletimepost30]	-0.00264	0.000	-0.00290	-0.00239
β4 [Sampletimepost30##Positive PHQ9]	0.00035	0.236	-0.00023	0.00093
β5 [Female]	0.19357	0.023	0.02725	0.35989
β6 [Daytype]	-0.06667	0.317	-0.19736	0.06402
β7 [Bleeding gums while brushing]	0.19736	0.089	-0.03001	0.42474
β8 [Use of ibuprofen/naproxen]	-0.12102	0.154	-0.28723	0.04519
log-likelihood	-820.8544			
AIC	1675.709			
BIC	1756.278			
ICC| person level	0.29021		0.17540	0.44008
ICC| sample day level	0.29021		0.17540	0.44008

Supplemental Table 6. Interaction of the slope of the morning rise of cortisol and suicide risk (log-transformed)

	Full model with morning rise slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive SBQ]	0.36463	0.026	0.04308	0.68269
β2 [Sampletimepre30]	0.00421	0.036	0.00056	0.00787
β3 [Sampletimepre30##Positive SBQ]	-0.00529	0.318	-0.01621	0.00563
β4 [Sampletimepost30]	-0.00258	0.000	-0.00282	-0.00235
β5 [Female]	0.21163	0.014	0.04818	0.37508
β6 [Daytype]	-0.07037	0.289	-0.20037	0.05964
β7 [Bleeding gums while brushing]	0.20702	0.068	-0.01518	0.42921
β8 [Use of ibuprofen/naproxen]	-0.10388	0.218	-0.26902	0.06127
log-likelihood	-791.458			
AIC	1616.915			
BIC	1697.343			
ICC| person level	0.28428		0.17007	0.43500
ICC| sample day level	0.28428		0.17007	0.43500

Supplemental Table 7. Interaction of the slope of the daily fall of cortisol and suicide risk (log-transformed)

	Full model with daily fall slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive SBQ]	0.28224	0.043	0.00900	0.55548
β2 [Sampletimepre30]	0.00367	0.039	0.00018	0.00717
β3 [Sampletimepost30]	-0.00257	0.000	-0.00282	-0.00232
β4 [Sampletimepost30##Positive SBQ]	-0.00015	0.697	-0.00088	0.00059
β5 [Female]	0.21234	0.011	0.04889	0.37580
β6 [Daytype]	-0.07004	0.291	-0.20005	0.05998
β7 [Bleeding gums while brushing]	0.20695	0.068	-0.01526	0.42916
β8 [Use of ibuprofen/naproxen]	-0.10372	0.218	-0.26888	0.06144
log-likelihood	-791.944			
AIC	1617.887			
BIC	1698.315			
ICC| person level	0.28534		0.17093	0.43607
ICC| sample day level	0.28534		0.17093	0.43607

Supplemental Table 8. Interaction of the slope of the morning rise of cortisol and suicide ideation (log-transformed)

	Full model with morning rise slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive SI]	0.15672	0.248	-0.10890	0.42235
β2 [Sampletimepre30]	0.00422	0.029	0.00044	0.00801
β3 [Sampletimepre30##Positive SI]	-0.00317	0.481	-0.01197	0.00564
β4 [Sampletimepost30]	-0.00258	0.000	-0.00282	-0.00235
β5 [Female]	0.21402	0.012	0.04682	0.38121
β6 [Daytype]	-0.07399	0.268	-0.20478	0.05681
β7 [Bleeding gums while brushing]	0.22168	0.054	-0.00380	0.44715
β8 [Use of ibuprofen/naproxen]	-0.12253	0.149	-0.28902	0.04397
log-likelihood	-821.501			
AIC	1677.002			
BIC	1757.571			
ICC| person level	0.28753		0.17301	0.43773
ICC| sample day level	0.28753		0.17301	0.43773

Supplemental Table 9. Interaction of the slope of the daily fall of cortisol and suicide ideation (log-transformed)

	Full model with daily fall slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive SI]	0.09563	0.405	-0.12968	0.32094
β2 [Sampletimepre30]	0.00369	0.038	0.00020	0.00718
β3 [Sampletimepost30]	-0.00259	0.000	-0.00285	-0.00233
β4 [Sampletimepost30##Positive SI]	0.00006	0.854	-0.00054	0.00066
β5 [Female]	0.21432	0.012	0.04713	0.38150
β6 [Daytype]	-0.07400	0.268	-0.20480	0.05681
β7 [Bleeding gums while brushing]	0.22164	0.054	-0.00382	0.44711
β8 [Use of ibuprofen/naproxen]	-0.12245	0.149	-0.28893	0.04403
log-likelihood	-821.731			
AIC	1677.463			
BIC	1758.032			
ICC| person level	0.28782		0.17318	0.43814
ICC| sample day level	0.28782		0.17318	0.43814

Supplemental Table 10. Interaction of the slope of the morning rise of cortisol and suicidal history (log-transformed)

	Full model with morning rise slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive LifeHist]	0.21001	0.033	0.01774	0.42342
β2 [Sampletimepre30]	0.00458	0.028	0.00049	0.00867
β3 [Sampletimepre30##Positive LifeHist]	-0.00437	0.216	-0.01129	0.00255
β4 [Sampletimepost30]	-0.00258	0.000	-0.00282	-0.00234
β5 [Female]	0.21663	0.010	0.05155	0.38171
β6 [Daytype]	-0.07509	0.260	-0.20564	0.05546
β7 [Bleeding gums while brushing]	0.20859	0.068	-0.01520	0.43237
β8 [Use of ibuprofen/naproxen]	-0.13038	0.122	-0.29563	0.03486
log-likelihood	-791.78			
AIC	1617.56			
BIC	1697.988			
ICC| person level	0.28767		0.17295	0.43817
ICC| sample day level	0.28767		0.17295	0.43817

Supplemental Table 11. Interaction of the slope of the daily fall of cortisol and suicidal history (log-transformed)

	Full model with daily fall slope interaction			
	Est	p value	95% CI	
Fixed effects				
β1 [Positive LifeHist]	0.12220	0.173	-0.05373	0.29812
β2 [Sampletimepre30]	0.00371	0.037	0.00023	0.00720
β3 [Sampletimepost30]	-0.00263	0.000	-0.00291	-0.00234
β4 [Sampletimepost30##Positive LifeHist]	0.00023	0.298	-0.00021	0.00067
β5 [Female]	0.21670	0.010	0.05166	0.38173
β6 [Daytype]	-0.07507	0.260	-0.20563	0.05549
β7 [Bleeding gums while brushing]	0.20779	0.069	-0.01592	0.43151
β8 [Use of ibuprofen/naproxen]	-0.12985	0.123	-0.29504	0.03534
log-likelihood	-791.823			
AIC	1617.646			
BIC	1698.073			
ICC| person level	0.28999		0.17490	0.44039
ICC| sample day level	0.28999		0.17490	0.44039

APPENDIX B
Chapter 4 Supplemental Tables

Supplemental Table 1. Relationship Between Evening CRP, Depression Screen, Suicidal Ideation, Suicide Risk, and History of Suicidality

Depression Screen	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 Evening CRP	1.00022	0.148	0.9999	1.0005
Pseudo R^2	0.0239			
Model significance	0.149			
Suicidal Ideation	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 Evening CRP	1.00015	0.314	0.9999	1.0004
Pseudo R^2	0.0106			
Model significance	0.329			
Suicide Risk	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 Evening CRP	0.9989	0.200	0.9972	1.00059
Pseudo R^2	0.0536			
Model significance	0.0589			
History of Suicidality	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 Evening CRP	0.9998	0.406	0.999	1.0002
Pseudo R^2	0.007			
Model significance	0.3636			

Supplemental Table 2. Relationship Between Diurnal CRP output, Depression Screen, Suicidal Ideation, Suicide Risk, and History of Suicidality

Depression Screen	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 CRP AUCg	1	0.061	1	1
Pseudo R^2	0.0387			
Model significance	0.0667			
*Suicidal Ideation**	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 CRP AUCg	1.00	0.045	1.00	1.00
Pseudo R^2	0.0474			
Model significance	0.0439			
Suicide Risk	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 CRP AUCg	0.999	0.395	0.999	1.000
Pseudo R^2	0.0157			
Model significance	0.3072			
History of Suicidality	**Bivariate Model**			
	OR	**p**	**95% CI**	
β_1 CRP AUCg	1.000	0.262	0.999	1.000
Pseudo R^2	0.0071			
Model significance	0.360			

*Sensitivity analyses revealed that one observation was likely driving this association. Once dropped from the model, significance dropped to p = 0.136.