DO AEROBIC EXERCISE AND MINDFULNESS ACT SYNERGISTICALLY TO MITIGATE PSYCHOLOGICAL DISTRESS IN COLLEGE STUDENTS EXPERIENCING HIGH LEVELS OF STRESS?

Gabriel Hart Zieff

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Approved by:

Anthony C. Hackney

Lee Stoner

Barnett Frank

ABSTRACT

Gabriel Hart Zieff: Do aerobic exercise and mindfulness act synergistically to mitigate psychological distress in college students experiencing high levels of stress?
(Under the direction of Anthony C. Hackney)

Purpose: To assess whether there is a synergistic beneficial effect of aerobic exercise (AE) and mindfulness meditation (MM), compared to effects of MM alone, on stress and related variables in high-stress young adults. **Methods:** 32 high-stress young adults were randomized to a four-week MM, AE+MM, or control intervention. Perceived stress (PSSQ), and anxiety/depression (DASSQ) were assessed at baseline, and after weeks 1 and 4. A randomized sub-sample from each group underwent physiological testing at baseline and post-intervention. **Results:** No significant interactions were found (PSS: p=0.12; DASS: p=0.21; heart rate: p=0.50; systolic blood pressure: p=0.90; diastolic blood pressure: p=0.16; arterial stiffness: p=0.90; heart rate variability: p=0.53). PSS and DASS decreased from baseline to post in MM (PSS: ↓27%; DASS: ↓43%) and AE+MM (PSS: ↓34%; DASS: ↓40%). Little change occurred in Control (PSS: ↓8%; DASS: ↓4%). **Conclusion:** MM may be as effective as AE+MM in combatting psychological distress in young adults.

To my family, friends, and Mother Nature.
Thank you for sustaining me.
May all that I do honor you.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AE	Aerobic exercise
ANS	Autonomic nervous system
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CAPS	Counseling and psychological services
CBP	cAMP response element binding protein
CRH	Corticotropin-releasing hormone
DASS	Depression Anxiety Stress Scales
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosterone
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HRR	Heart rate reserve
HRV	Heart rate variability
IL-6	Interleukin-6
MBI	Mind-body intervention
MBSR	Mindfulness-based Stress Reduction
MM	Mindfulness meditation

Nf-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PFC	Prefrontal cortex
PNS	Parasympathetic nervous system
PSS	Perceived Stress Scale
QPS	Questionnaire for Psychological and Social Factors at Work
RMSSD	Root mean squared of the standard deviation
RPE	Rate of perceived exertion
Rx	Prescription medication
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
SRC-1	Steroid receptor coactivator-1
SSRI	Selective serotonin reuptake inhibitor

CHAPTER I: INTRODUCTION

The pace, pressure, and socio-political landscape of contemporary Western society is conducive for high levels of stress. Chronically elevated levels of stress contribute to psychological and physiological disorders such as anxiety, depression, and cardiovascular disease.[1,2,3] Thus, there is a need to examine techniques that can reduce stress, regulate the stress pathways, and prevent the development of stress-related states. Aerobic exercise (AE) and mindfulness meditation (MM) each promote psychological health[4,5]. MM consists of several executive and behavioral components, but can simply be defined as "moment-to-moment, non-judgmental awareness."[6] However, it is unknown if, when integrated, MM and AE have a synergistic effect on stress reduction and associated psychophysiological variables.

Stress stimulates the sympathetic branch (SNS) of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis to assist in the response and recovery from stress.[7] However, with chronic exposure to stress, dysregulation of these pathways occurs, which is thought to contribute to psychological and physiological disorders by causing inflammation, autonomic dysfunction, as well as maladaptive changes in brain structure and function.[8]

AE and MM are thought to decrease levels of stress and stress-related symptomology by regulating the SNS and HPA pathways, which likely occurs due to improvements in stress appraisal, buffering, and coping.[9,10,11] One way the latter has been assessed is through the measurement of the ratio of cortisol to dehydroepiandrosterone (DHEA) -another hormone that binds to the glucocorticoid receptor.[12,13]

It appears no study has yet examined the combined effects of AE and MM, as compared the effects of just one of the activities, on psychological well-being and stress-related symptomology. Therefore, the present research is undertaken. The purpose of this study is two-fold. The first is to assess whether there is a synergistic beneficial effect of AE and MM, as compared to the effects of MM alone, on psychological wellness and stress-related psychophysiological symptomology in individuals with initial high levels of stress. Second, by comparing the individual effects of MM versus a combination of AE and MM on stress and related symptoms, the intent is to begin elucidating mechanistic similarities and differences in each behavior's stress-reducing properties.

It is hypothesized that there will be an additive beneficial effect of AE and MM, as compared to the effects of MM alone, on stress-related psychophysiological parameters in college students experiencing high levels of psychological stress.

CHAPTER II: REVIEW OF LITERATURE

Stress – What is it?

Stress can be described as "a real or perceived state of threatened homeostasis."[14] Exposure to stressors and the stress response has been defined as the "allostatic load." [15] All organisms, including humans, experience stress. Stress is a ubiquitous term, but it is commonly understood as a solely negative experience. This section will briefly highlight the beneficial effects of "normal" or moderate exposure to stress, the maladaptive effects of stress when the "allostatic load" becomes too great, as well as the prevalence of stress in society today.

Stress is a normal and often adaptive human experience. [16] For example, AE places a stress on the cardiovascular system, which leads to positive adaptations such as reduced heart rate (HR) and improved oxygen utilization.[17] Similarly, in the case of psychological stress, moderate exposure to mental, cognitive, or psycho-social challenges (i.e., academic exams, social events) may improve performance when future challenges arise[18].

However, while "normal" or occasional stressors promote beneficial adaptations, repetitive exposure to high levels (or intensities) of stress, whether psychological or physiological in nature, is thought to induce negative psychological and physiological states.[18] The harmful physiological effects of stress can be traced back to the work of Hans Seyle and his proposed "General Adaptation Theory," in which decreases in the ability to respond to and recover from stress cause a cascade of unfavorable endocrine consequences.[19] In this schema, stressors may be categorized as either a eustress (positive) or distress (negative)[20].

Given the conduciveness for high levels of stress in today's society, it is not surprising

that the majority of Americans report high levels of stress, and the prevalence of high levels of stress are increasing nationwide. For example, in 2015, 24% of Americans reported "extreme" levels of stress, up from 18% in 2014[21]. Data from the same study also showed that over one third of Americans reported that their stress levels had increased from the previous year[21]. Examples of daily psychological stress that have been associated with negative health outcomes include work-related stress[22], marital stress[23], racial discrimination[24], and caring for a sick spouse[25].

In addition to the general adult population, young adults, and in particular college students, often report high levels of stress. The transition to college is arguably the most significant transition that occurs in young adults. New academic, social, and economic stressors, among others, are major causes of stress in this population. Importantly, the 2011 National College Health Assessment from the American College Health Association found that among American college students: 86% felt overwhelmed, 81% felt exhausted, 30% felt too depressed to function, and 6.6% had seriously considered suicide.

Specifically, high levels of psychological stress, over time, leads to increased risk of developing chronic psychological states such as anxiety, post-traumatic stress disorder, and depression[26,27]. Physiologically, chronic stress may impair immune function[28], cause inflammation[29], and confer cardiovascular disease risk[30]. Randomized clinical, longitudinal, and animal studies have also demonstrated a range of negative outcomes associated with stress beyond the most commonly reported depressive and anxiety-related states[30,31,32]. These include, but are not limited to, decreased quality of life and worse outcomes in individuals with chronic illnesses[23,33], decreased telomere length[34], tumor growth[35], increased susceptibility to infection[1], increased sedentary behavior[36], poor sleep quality[1], overeating[37,38], and substance dependency[39].

Interestingly, chronic physical stress (i.e. sport-related overtraining) and chronic psychological stress (i.e. care-giving) induce largely similar effects such as increased negative affect[7,40], fatigue[41,42], and weakened immune responses[43,44] , suggesting activation of similar stress pathways. While different mechanisms have been proposed, excessive stress is most often thought to set the stage for psychological and physiological disorders by impairing the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and neural structure and function.[1,26,45]

Stress Physiology and Pathophysiology

Homeostasis and Stress

The stress response globally impacts physiology as the body attempts to return to homeostasis. That is, many physiological functions are affected by stress, or more accurately, the mediators of the stress response. Specifically, responses of the SNS, HPA axis, and neural networks affect a variety of processes including energy metabolism, growth, reproduction, immunity, and behavior[7]. As mentioned previously, the initial SNS response to stress is termed the "fight or flight" response. Not surprisingly, the goal of this response is to "respond" or "recover" from the threat to homeostasis by prioritizing only the most essential functions and systems. For example, in the face of a threat, time-sensitive adaptive functions are prioritized such as increased arousal, awareness, and oxygenation of brain, cardiac, and skeletal tissue[7]. This occurs at the expense of non-adaptive processes such as reproduction, digestion, and growth[7]. Occasional or "normal exposure to stress, and subsequent transient shifts to prioritize essential processes at the expense of non-essential processes are not necessarily unhealthy, and as detailed earlier, can be adaptive.

However, as is the case with many physiological systems, the homeostatic stress response can be described as having a dose response characterized by an inverted "U-shaped" curve. Simply put, moderate exposure to stress and the stress response helps an organism to function at its most optimal level, whereas too little or too much exposure to stress and the ensuing response is maladaptive. This concept, along with the "triaging" of essential physiological systems that takes place, serve as the basis for understanding the detrimental, and potentially pathological, effects of chronic stress. The following sections will summarize the basic physiology of the primary stress pathways and explain how impairment of these pathways as a result of chronic stress sets the stage for physiological and psychological disease.

The Sympathetic Nervous System

The body's initial response to acute stress is through the sympathetic branch of the ANS[46]. The SNS stimulates the secretion of the catecholamines epinephrine and norepinephrine from the adrenal medulla and sympathetic nerves[15]. In conjunction with the HPA axis, the SNS-mediated rise in catecholamines induces the "fight or flight" response by increasing HR and cardiac contractility, as well as inducing changes in vessel diameter[15]. Unremittent exposure to the "fight or flight" decreases the capacity of the parasympathetic nervous system (PNS) to moderate sympathetic activity both at rest and in response to stress[47]. The effects of stress on sympathovagal balance, the relative balance of SNS and PNS influence, is typically assessed using blood pressure (BP), heart rate (HR), and heart rate variability (HRV).

The Hypothalamic-Pituitary-Adrenal Axis

The HPA axis is the major neuroendocrine "stress" pathway and exerts its influence at both central and peripheral levels[7]. This axis regulates the release of several important hormones in response to stress including vasopressin, also known as anti-diuretic hormone, and

corticotropin-releasing hormone (CRH)[48]. The latter is secreted from the hypothalamus, triggering the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, ultimately stimulating the adrenal gland to secrete the critical signaling molecules in the stress response of the HPA axis, cortisol and DHEA[7].

Cortisol

By binding to mineralocorticoid and glucocorticoid receptors, cortisol helps the body respond to stress by increasing energy availability through gluconeogenesis, glycogeneolysis, and lipolysis, and helps to suppress non-essential bodily functions[20,49]. Furthermore, cortisol has anti-inflammatory and immunosuppressive properties that help ensure that the body is not incapacitated by excessive immune or inflammatory responses in the face of a threat or injury[50]. While these processes may be necessary for eventual and adequate recovery, mitigating these responses acutely enables the short-term ability to escape from or deal with the stressor. Lastly, it is critical to highlight the normal pulsatile action of cortisol. While cortisol is at its highest in the morning following waking, as the body prepares for the stressors of the day, levels fall throughout the afternoon with the lowest levels typically occurring in the evening[51].

Importantly, cortisol inhibits the release of CRH from the hypothalamus and ACTH from the anterior pituitary[7,20]. CRH normally stimulates the anterior pituitary to secrete ACTH, which acts on the adrenal cortex to release cortisol[7,20]. Thus, cortisol's inhibitory effect on CRH is a self-regulating negative-feedback mechanism that prevents excessive release of cortisol[7]. However, with elevated exposure to and/or intensity of stressors this feedback loop becomes disrupted. While high levels of stress initially result in hyperactivity of the HPA axis, overtime, disruption of the said feedback loop may cause a shift to a hypoactive axis and a flattening of the cortisol rhythm[1,8].

Due to its critical and extensive role in mediating the body's response to stressors, as well as its ability to be measured in blood, saliva, and hair samples, cortisol is commonly used as a marker of the stress response. Elevated resting and post-acute stress levels are traditionally understood as reflecting a greater degree of stress and/or an inability to cope. However, given the understanding that blunted resting cortisol levels or a flattened daily cortisol rhythm may also occur as a result of chronic stress, the "higher stress equals higher cortisol" dogma does not always hold true.

Dehydroepiandrosterone

In addition to its role as a precursor to the production of sex hormones, DHEA, like cortisol, has wide-ranging effects on many physiological systems including neurotransmitter activity, immunity, and cognitive function[12]. However, while cortisol and DHEA are both derivatives of the HPA axis, the latter lacks the strong diurnal rhythm seen with cortisol and has largely opposing regulatory actions[12,52]. For example, human and animal studies have demonstrated that the neurotoxic effects and dysregulated immune response associated with hypercortisolism are diminished in the presence of higher levels of DHEA[53,54,55]. Thus, higher levels of DHEA may be indicative of a greater ability to return to homeostasis in the face of a stressful challenge, or in other words, may reflect enhanced psychophysiological resilience or coping[12].

Although it must be noted that compared to cortisol the role of DHEA in stress-related pathophysiology is not as well understood, there has been recent interest in examining the ratio of DHEA to cortisol as a marker of adrenocortical activity. Given that the hormones both originate from the HPA axis, exert their influence on many of the same psychophysiological

systems, and yet have antagonistic actions may suggest that the ratio is a more sensitive marker of HPA function, stress load, and stress coping capacity than cortisol alone[56].

Neural Networks

In addition to the HPA axis and ANS, several other interrelated neural pathways and structures are involved in the stress response. These include serotoninergic and dopaminergic systems, as well as the hippocampus, and the amygdala[56]. Together, they help govern emotion, cognition, fear, anger, and reward processing, all of which contribute to an individual's perception of, and response to psychological stress[56]. Importantly, activation of the amygdala, or the "fear processing center" of the brain, stimulates CRH secretion, and thus contributes to cortisol release by the adrenal cortex[56]

Systems Summary: Coordinated and Multi-Directional Pathways

In conclusion, it is important to reiterate that these are not isolated systems. They are intimately intertwined in a highly complex, multi-directional network of positive and negative feedback loops that are continuously communicating. For example, one way in which the SNS responds to stress is by releasing the pro-inflammatory cytokine interleukin-6 (IL-6) which in turn activates the HPA axis[57,58]. Similarly, stress-induced activation of the HPA axis stimulates release of catecholamines from the adrenal medulla.[3] In sum, while a full discussion of the interplay between these systems is beyond the scope of this review, it is critical to have a proper conceptual understanding of the stress response as global and coordinated.

Together, the HPA axis, SNS, and neural networks target cognitive, emotional, endocrine, gastrointenstinal, cardiometabolic, and immune systems. Not surprisingly, any impairment of these pathways, which may take place as a result of chronic stress, has a domino effect on parallel systems, possibly setting the stage for psychological and physiological disease.

The following sections will provide background information on the relationship between psychological stress and disease, as well as outline the major detrimental effects that chronic stress has on immune systems, autonomic, and psychological systems.

Chronic Stress and Disease

The relationship between stress and disease is not a new concept. Physicians, researchers, and philosophers have acknowledged the connectedness of mind and body functioning for hundreds, if not thousands, of years. Despite this understanding, the collection of evidence supporting this association, particularly with ample methodological rigor, is in its relative infancy. While a number of studies have demonstrated cardiovascular[59,60], metabolic[61,62], and immune[44,63] responses to acute stress that are associated with disease risk, they are only speculative in the sense that it is unknown if these responses would become chronic and true "risk factors" if stress persisted overtime.

Some of the strongest evidence to support the notion that chronic stress promotes disease can be found in a growing body of longitudinal and cross-sectional studies showing relationships between depressive symptoms and cardiometabolic risk[64,65,66,67]. For example, a meta-analysis found that diabetic individuals were twice as likely to have comorbid depression than a non-diabetic comparison group[68]. However, these studies do not demonstrate causal direction. Thus, stating that stress leads to depression and/or that depression leads to cardiometabolic disease cannot be made conclusively at present. On the other hand, there does seem to be consensus on two important points regarding stress and disease: [1] the primary pathways damaged by chronic stress are the HPA axis, SNS, and neural processing networks, and [2] decreased function in these systems as a result of chronic psychological stress may induce pathogenic changes in

immune, cardiometabolic, and neuropsychological systems[12,29,28]. Figure 1 illustrates the inter-related factors thought to mediate the relationship between stress and disease.

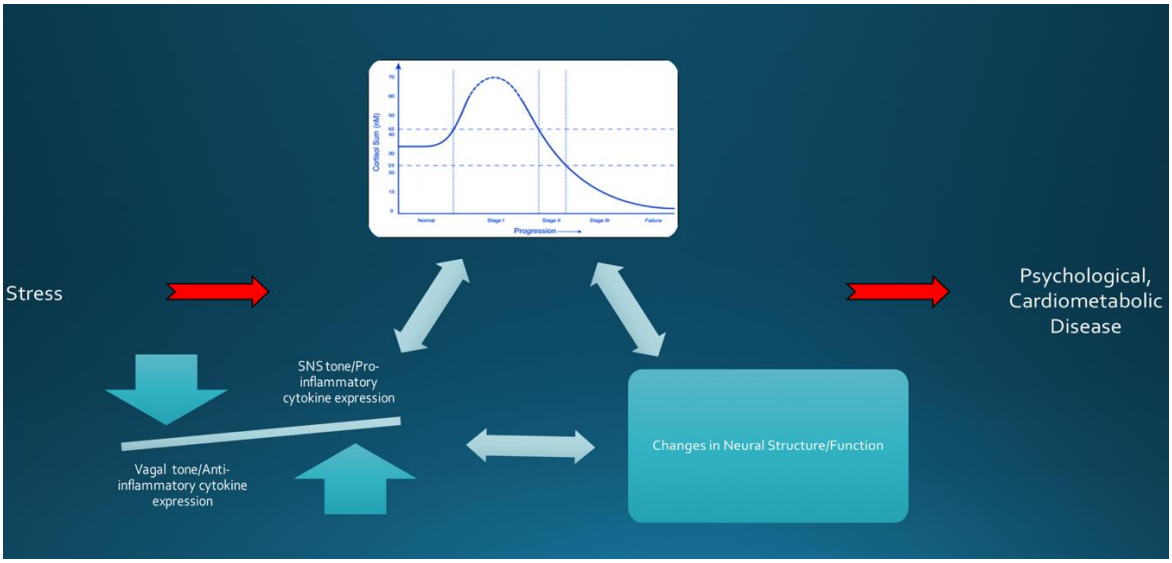

Figure 1. Proposed pathogenic mechanisms of psychological stress.

Immune Dysfunction

Disordered HPA and SNS pathways as a result of chronic stress are thought to contribute to changes in immune function that can effect health. The excessive stimulation of cortisol and catecholamines associated with chronic stress affect immune cell trafficking, differentiation, effector function, proliferation, antibody production, cytolytic activity, and expression of cytokines, chemoattractants, and adhesion molecules[28,69,70,71].

In the case of chronic HPA axis activation, excessive cortisol released into the circulation is able to bind to a variety of glucocorticoid receptors found on immune cells throughout the body[28]. Elevated cortisol levels repress Nuclear Factor-kb (NF-kB) activity, possibly by inhibiting its translocation to the nucleus or by causing competition between the glucocorticoid receptors and NF-kB for critical cofactors such as CBP (cAMP response element binding protein) and SRC-1 (steroid receptor coactivator-1).[72,73,74] NF-kB regulates the activity of

cytokine-producing immune cells including macrophages and CD4+ T-helper cells[75]. Elevated glucocorticoid release has also been associated with loss of lymphoid, splenic, and thymic tissues, which further impairs immune cell production and impairs leukocyte trafficking[1]. These changes in immune function increase susceptibility to infection and neoplasm[1]. Not surprisingly, stress-induced hypercorticolism may also lead to, or perpetuate auto-immune disease[48].

As mentioned previously, while initial high levels of stress commonly result in hyperactivity of the HPA axis, prolonged exposure to stressors may result in diminished HPA activity, and hypocorticolism[1]. For example, blunted cortisol responses are commonly reported in depressed individuals[3]. Blunted cortisol responses, like elevated responses, have a deleterious effect on the immune system and, in particular, shift immune function to favor a pro-inflammatory state[161]. Higher levels of inflammation have been associated with the flattening of the daily cortisol rhythm seen in individuals with chronic stress-related psychological states[76]. While a normal cortisol response has an immunosuppressive and anti-inflammatory effect, a blunted response and/or flatter diurnal rhythm likely promotes inflammation by allowing pro-inflammatory cytokines to go unchecked.[1,61]

Interestingly, while the HPA axis and SNS function in concert in responding to stressors, the two systems have conflicting roles in certain instances. For example, the former's release of cortisol normally functions as immunosuppressive and anti-inflammatory, whereas catecholamine release by the SNS has a largely inflammatory (i.e., immunostimulatory) effect[56,28]. Catecholamines influence immune function by targeting adrenergic receptors located on a variety of immune cells including lymphocyctes, and machrophages[28]. The B-adrenergic receptors, in particular, are involved in SNS-mediated changes in immune function[77]. Stimulation of the B-adrenergic receptor by catecholamines activates a G-protein complex which

subsequently promotes the synthesis of cAMP from adenosine triphosphate (ATP).[28] Ultimately, this causes inhibition of mast-cell degranulation, while stimulating the release of IL-6 and other pro-inflammatory cells through changes in cytokine gene expression[78,79].

In sum, the activation, and in some cases, under-activation, of the HPA axis and SNS have diverse effects on immune functions relating to immune cell production and expression. Although some precise mechanistic components of the ways in which the stress pathways interact with the immune system are not fully understood, it is clear that these interactions can and do significantly impact human health, likely through causing a maladaptive shift towards a pro-inflammatory state. Not only is it well established that a wide range of diseases, ranging from atherosclerosis to irritable bowel syndrome, stem from, or are significantly perpetuated by, immune dysfunction and inflammation, but many of these same disorders are associated with high levels of stress and chronic stress-related states such as depression and anxiety[1,7,80,81].

Cardiometabolic Dysfunction

In addition to, and in part as a result of immune dysfunction, various components of cardiometabolic systems are also negatively affected by chronic stress and may contribute to pathological states. In particular, persistent stressors have been shown to induce maladaptive changes in autonomic, and endothelial function[15,29,60].

Autonomic Imbalance

As outlined previously, the SNS is one of the primary human stress pathways. Unsurprisingly, stress-induced sympathetic hyperactivity diminishes the ability of the PNS to dampen the excitatory cardiovascular effects of the SNS. This causes an imbalance of the SNS and PNS, which is thought to contribute to increased cardiometabolic risk and possibly neuropsychological dysfunction by increasing inflammation. Specifically, increases in resting

HR, and decreases in HRV have been reported in populations experiencing high levels of stress, who also present with high levels of inflammatory cytokines such as IL-6[15,82]. Further, PNS tone is decreased both at rest and following acute stress in individuals with chronic stress[15,82].

While there is considerable agreement that maladaptive changes in these parameters contribute to cardiometabolic risk and are associated with negative stress-related states, it is unclear precisely how they are also implicated in stress-mediated psychopathogenesis[83,84]. However, several points can be confidently stated. First, it is clear that autonomic dysfunction is associated with increased inflammation which in turn stimulates the HPA axis[47,85,86]. Second, both the SNS and HPA axis are typically dysregulated in individuals with stress-related psychological disorders.[3,8,87] Thus, it is fair to state that disruption in these systems are likely key mediators of the relationship between stress and psychological disease[88]. Last, these points provide an excellent example of the complex and bi-directional nature of the stress pathways[86,89,90,91].

Endothelial Dysfunction

Stress may also promote disease by causing endothelial dysfunction, one of the major causes of atherosclerosis and cardiovascular disease. Stress may lead to endothelial dysfunction by decreasing nitric oxide, which interestingly may be a result of the increase in catecholaminergic activity discussed in previous sections[60]. Nitric oxide is a critical vasodilator, anti-oxidant and regulator of platelet and monocyte adhesion in the endothelium[60]. Reduced formation of, or increased degradation of nitric oxide promote free-radicals and accumulation of platelets and monocytes on the endothelium, which are thought to lead to atherosclerosis[60].

Most of the recent research examining stress and endothelial function have assessed the latter by measuring arterial stiffness[60]. Although not all of the evidence is in agreement, both

acute and chronic stress seem to negatively impact endothelial function[60,30,92]. For example, both the chronic stress associated with caregiving and acute laboratory stressors have been associated with decreased arterial stiffness[60,92]. Findings that endothelial function is impaired as a result of both acute and chronic stress offer the possibility that the endothelial dysfunction associated with chronic stress is a product of numerous, and potentially compounding acute stressors, each of which has an immediate and detrimental effect on the endothelium.

Neuropsychological Dysfunction

One of the most well-established consequences of high levels of stress is psychological dysfunction and subsequent mental illness.[93,94] Psychological dysfunction and mental illness are broad terms that encompass a wide range of subjective and objective components. This dysfunction or illness can be described as a clinically significant behaviorally, biologically, or psychologically derived syndrome associated with distress, disability, or suffering that is not expected or related to a "culturally sanctioned event" (i.e. death of loved one).[95] It is likely that the said changes in behavior, cognitive function, and affect that often occur in parallel with high levels of stress both influence the progression of, and are perpetuated as a result of stress-based psychological impairment[24,32,94,95]. While the precise mechanisms of this relationship are currently unclear, there is general consensus that stress promotes neuroinflammation[31,96]. This may lead to subsequent elevations in microglial activity and atrophy of various brain regions, leading to psychological disease[33,97].

Augmentation of inflammatory cytokine expression as a result of stress-induced glucocorticoid release in the brain has been associated with damaged cortical microglia.[32,98] Microglia are myeloid cells that function as the primary component of the central nervous system's adaptive immune response.[96] Increased levels of microglia activity have been

associated with psychological disorders known to be associated with psychological stress[96]. For example, changes in microglial markers have been observed in several psychological disorders such as depression[99], anxiety[100], schizophrenia[101], and autism spectrum disorders[102]. Thus, increased microglia may prime the onset of mental illness by promoting maladaptive structural and functional changes that impair neural networks' ability to regulate executive and emotional processes[98]. Specifically, augmented microglial activity have been shown in post-mortem regions including the dorsal anterior cingulate, dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, and mediodorsal thalamus of individuals who were depressed, and in the ventral pre-frontal white matter in those that had committed suicide[33]. Similar findings were demonstrated in rodent studies using animal models of stress and depression[33]. Further, reduced volume of many of these same regions, particularly in frontal and limbic areas, have been shown in both animals and human studies assessing the neurological effects of psychological disease (or models of psychological disease in the case of animal studies)[33,103,104,93]. Interestingly, *increased* volume of the amygdala has also been associated with high levels of stress, possibly signifying an increased propensity or susceptibility to experience fear and negative affect[105].

Several final points are appropriate to bring up prior to concluding. First, it must be reiterated that though it is likely that the mechanisms described above are implicated in stress-induced psychopathology, exact mechanisms are still unclear and other, albeit related theories exist. Other possible factors involved in stress-induced psychological disease include decreased cranial blood flow and metabolism, and increased excitatory amino acids, oxidative/nitrosative products, and activation of transcription factors[31]. Next, it must be highlighted that both the developing and aging brain seem to be more vulnerable to stress in regards to stimulating negative effects on neuroinflammation, brain volume, and coordination of neural pathway[96,31].

Taken together, while the exact contribution of psychological stress to the pathogenesis of mental illness is not clear, neuroinflammation and subsequent deterioration of various brain functions controlling executive and emotional networks appear to have significant involvement. High levels of psychological may be most likely to promote these maladaptive responses during early and late periods of the lifespan. Despite the deleterious effects of psychological stress, the risk associated with this variable can be modified through lifestyle behaviors. The following sections will describe the field of stress-reduction, and in particular highlight two promising lifestyle behaviors – aerobic exercise and mindfulness meditation - as therapeutic options that may be feasibly used to mitigate the harmful effects of psychological stress.

Stress-Reduction

Given the pervasiveness of high levels of stress in today's society, and the growing understanding of the toll that stress takes on physiological and psychological function, it is not surprising that stress reduction techniques often employ both mental and physical components and are considered to be a beneficial aspect of maintaining a healthy, and well-balanced life[106]. Techniques such as such as yoga, tai chi, and qi gong have shown varying improvement in subjective psychological measures of well-being such as perceived stress and occasionally physiological measures such as blood pressure[107,108,109]. However, research assessing the effects of stress-reduction on health is in its relative infancy, and most prior studies suffer from poor methodological quality, limiting the ability to confidently recommend stress-reduction interventions[110]. Moreover, in many of the stress-reduction techniques involving both physical and mental components, when effects have been reported, it is difficult parse out which component caused the observed effect.

On the other hand, AE and MM have gained increasing attention as activities with stress-reducing properties and promote both physical and mental health[6,111,112]. Additionally, they are characterized by distinct and specific properties that can be more easily controlled than traditional mind-body techniques such as yoga, tai chi or qi gong. Further, AE and MM can be feasibly implemented in research and clinical settings. Of note, there is evidence suggesting that both AE and MM have the same depression-reducing effect as a standard pharmacological anti-depressant, such as a selective serotonin reuptake inhibitor (SSRI).[113,111,114] The following sections will describe AE and MM in more detail, summarize the state of the literature in regards to their stress-reducing capacities, and justify the need for the proposed study.

Aerobic Exercise

AE consists of repetitive sub-maximal contractions of large muscle groups for a continuous duration. There is now substantial evidence demonstrating numerous mental health benefits of moderate-intensity AE including reducing symptoms of stress, anxiety, and depression, while promoting relaxation and improved cognitive performance[10,115,116]. Importantly, AE has been shown to promote reductions in depressive symptoms and relapse rates to the same extent as a pharmacological therapy[115,116,117,118]. Moreover, there is not only strong evidence for mental health improvement in psychiatric populations, but also in healthy populations regardless of age and gender[118,119]. However, it should be noted that some studies have shown *greater* anti-depressant and cognitive improvements from AE in males and young individuals, respectively[120,121]. Finally, numerous animal studies have consistently demonstrated improvements in a number of neurological outcomes in response to AE[122,123].

Despite these encouraging findings, there is still debate as to the optimal duration, intensity, and frequency of AE for improvement in stress-related psychological parameters. This

is due to a large degree of variation in exercise protocols of relevant studies, as well as poor methodological descriptions of the exercise protocol. When characteristics are given in these studies, they typically range from 20-90 minutes in terms of duration, 50-60% of maximum heart rate (HRmax) or "moderate" in terms of intensity, and from 2-4 days per week for 8-26 weeks in terms of frequency[115]. However, AE does seem to have a dose-related effect on stress-related symptoms, though some studies have reported ceiling effects with intervention durations lasting longer than 12 weeks[115]. Taken together, it seems likely that any AE is better than none in terms of promoting psychological health.

Besides improvements in psychological parameters, stress-related physiological benefits of AE have been demonstrated including improved resting and post-acute stress cardiovascular and autonomic function as measured by BP, HR, HRV, and arterial stiffness[124,125,126,127]. Though less consistently reported than autonomic measures, neuroendocrine factors related to stress have also been shown to be affected as a result of AE. For example, greater aerobic fitness has been associated with decreased HPA reactivity in response to a lab-stressor in both animals and humans[11,128]. While it is thought that the physiological improvements observed as a result of AE contribute to its positive effect on psychological health, it may also be the case that these autonomic and neuroendocrine effects occur, at least in part, *because* of the improvement in stress and mental health parameters. It is likely that the relationship is bi-directional.

In addition to the notion that improvements in autonomic and endocrine function mediate the effect of AE on stress and psychological health, several other factors, largely regarding brain structure and function, are thought to help regulate this effect. The most common hypothesis is AE-induced neurogenesis – or the development of new neurons – specifically within the hippocampus[117]. Indeed, animals given the opportunity to run have approximately double the

hippocampal neurogenic potential than their sedentary counterparts via increased cell proliferation, differentiation, and survival[122]. Specifically, long term running in male rodents increases dendritic length, complexity, and spine density within the pre-frontal cortex and hippocampus[118]. Further, increases in brain derived neurotropic factor (BDNF) – a neurotransmitter critical in neuronal maintenance, survival, and neuroplasticity, have been reported in human blood and animal brain regions such as the dentate gyrus in response to AE[118]. Interestingly, decreased levels of BDNF in the hippocampus and PFC have been associated with stress-induced hypercorticolism and has been hypothesized to play a role in the development of depression[118]. In the same vein, increases in BDNF are thought to play a critical role in the action of anti-depressants[118].

Given the increased volume of frontal and limbic structures, as well as the increase in cognitive function associated with AE, it is likely that increased neurogenesis underlies this structural change, and contributes to the stress-moderating/anti-depressant effect of the activity. However, animal studies provide the bulk of the evidence supporting AE-induced neurogenesis, as it is not currently possible to measure neurogenesis in humans. Thus, it must be stressed that though promising advances have been made in elucidating the neuropsychological mechanisms underlying AE-induced improvement in various mental health parameters, these ideas remain theoretical. Other neurological effects of AE that may contribute to its beneficial effect on stress and mental health include AE-induced inactivation of cortisol by converting it to its inert form – cortisone, endocannabinoid regulation of the amygdala (which may further promote BDNF), and changes in serotonin and dopamine levels[10]. While a full description of these potentially neuro-protective effects of AE is beyond the scope of this review, the reader is directed to reviews by Heijnen et al, Chen et al, and Tarumi et al.[10,118,129]

Mindfulness Meditation

Mindfulness can be described as non-judgmental, moment awareness[6]. It has been proposed to have five primary components including observing, describing, non-judging, acting with awareness, and non-reactivity[130]. Mindfulness Based Stress Reduction (MBSR) is the most commonly implemented and researched mindfulness intervention. It is an 8-week program designed for adults suffering from high levels of stress and stress-related illnesses[6]. The program consists of 2.5 hours of instructed mindfulness in a class setting once per week, and 45 minutes per day of self-based practice the remaining six days of the week[6]. It is important to note that the magnitude of stress reduction has been highly correlated to the degree of compliance in both research and clinical settings[6]. The following section will detail the specific psychological and physiological parameters that have shown improvement with MBSR and other mindfulness-based interventions (MBI's), as well as the hypothesized mechanisms leading to such effects.

MM has been shown to be an effective stress-reducing behavior, with most studies reporting improvements in psychological measures such as perceived stress and depressive symptomology[113,131,132,133]. In terms of stress-related physiological measures, MBI's have most notably demonstrated reductions in BP, but not to the same degree as AE[133,134,135,136]. MBI's have shown some improvements in the diurnal cortisol rhythm and autonomic shifts toward increased parasympathetic tone[137,37,138,139]. Furthermore, some evidence suggests that MM, like AE, may improve the return to allostasis following exposure to acute psychological stressors in variables such as blood pressure and cortisol, illustrating its possible dampening effect on neuroendocrine and cardiovascular responsivity to stress [133,140]. However, prior to commencing discussion on the putative mechanisms of MM, it must again be reiterated that studies employing mindfulness

based interventions (MBI) are in its infancy and often lack methodological rigor. Thus, at present we are unable to confidently state what the full stress-reducing capacity of MM is (or isn't).

Despite the inferior quantity and quality of evidence supporting MM as a stress-reducing strategy as compared to AE, it does seem likely that several of the same mechanisms may be at play. As explained above, MM has been linked to improvements in autonomic and neuroendocrine function. Similar to the stress-reducing effects of AE, the autonomic and neuroendocrine improvements associated with MM is likely both a cause of, and a result of the observed improvement in stress. The proposed stress-reducing mechanisms of MM are also similar to AE in the sense that they are thought to include neuroprotective effects such as to increased neuroplasticity and hippocampal volume[131,135,105]. Further, decreases in perceived stress following MM have been correlated to reductions in amygdala volume[109]. It has been proposed that such changes may increase connectivity in neural networks important for cognitive and behavioral processing. For example, advanced practitioners of MM showed increased functional connectivity of regions controlling mind-wandering and executive control both at rest and during MM[131]. This may influence emotion regulation and stress resilience as greater executive activation and integration of executive centers have been associated with decreased pain, negative affect, and stress[141,142,143]. Further, functional coupling of the posterior cingulate cortex, responsible for mind-wandering, and the left dorsolateral pre-frontal cortex which regulates top-down executive function was shown to occur in just eight weeks of MM within an unemployed population experiencing high levels of stress[131]. Recall that stress-related neuro-inflammation in several of these structures within fontal and limbic regions have been associated with psychological disorders [98,117,144].

Lastly, it must be noted that MM may indirectly promote stress-reduction by increasing levels of AE and physical activity[134]. As has been reported with other lifestyle behaviors such as diet, smoking, and alcohol consumption, the cognitive, emotional, and behavioral changes that are associated with MM may promote increased levels of AE, which in turn may contribute to its stress-reducing effect[134]. Similarly, AE has been proposed to increase levels of trait, or dispositional mindfulness by increasing awareness of one's bodily sensations[9]. Taken together, while it can be fairly confidently stated that MM and AE each induce beneficial, disparate effects on stress, these activities may also influence each other in a bi-directional manner, which could contribute to the stress-reducing effects.

Literature Summary

In conclusion, several points should be emphasized. First, while the precise mechanisms are not fully understood, it is widely understood that chronic stress has a maladaptive effect on psychological and physiological functioning. It is likely that these maladaptive effects are a result of dysfunctional stress-pathways, which may subsequently lead to impairment of immune, cardiometabolic, and neuropsychological systems. Second, the stress-reducing capacity and optimal prescription of AE and MM for stress reduction remains unclear. Third, the precise interplay of mechanisms mediating the relationships between AE, MM, stress-reduction, and health are largely speculative at present. Finally, despite these shortcomings, it does seem likely that changes in autonomic, endocrine, and neural function are the driving factors behind the stress-reducing capacities of AE and MM. Based on the information presented within this review, the following section will introduce the current study, justify its purpose, and propose a hypothesis.

Study Rationale and Purpose

Given the understanding that AE and MM have beneficial stress-reducing effects and the lack of understanding of the mechanisms behind these effects, it can be argued that these activities should be further explored in the context of promoting psychological well-being. Further, AE and MM are distinctly physical and mental activities, respectively, with specific and definitive characteristics. Thus, interventions utilizing these activities can offer several advantages over stress-reduction studies employing more traditional stress-reduction/mind-body activities such as yoga and tai chi. First, methodologies utilizing AE and MM can be more easily described and reproduced due to (1) their defined variables (i.e. AE: frequency, intensity, duration; MM: frequency, duration, specific cognitive-behavioral components) and (2) their non-overlapping of mental and physical components (i.e. AE does not include mental activities and MM does not include physical activities). Second, this ability to more precisely regulate what properties should be included and controlled for in an AE or MM study (i.e. duration and frequency) allows the researcher to more clearly deduce the causes of an observed effect.

With these advantages taken into consideration, there lies one additional opportunity, which is to assess whether there is a synergistic stress-reducing effect of an integrating AE and MM, by comparing an integrated AE + MM protocol to a MM-only protocol. Doing so would not only help to elucidate the similar and differential contributing factors of the stress-reducing effects underlying each activity, but also to help inform clinical practice and recommendations for physical and mental health practitioners.

CHAPTER III: METHODOLOGY

Participants

A total of 32 (27 F, 5 M) undergraduate and graduate students experiencing high levels of psychological stress at the University of North Carolina Chapel Hill (UNC) completed this study. Participants were eligible if they met one of the following criteria: they (1) were seeking mental health support from the UNC Counseling and Psychological Services (CAPS), (2) were currently, regularly taking an anti-depressant or anti-anxiety medication (i.e. Selective Serotonin Reuptake Inhibitor), or (3) scored 4-5 on single-item question of the Nordic Questionnaire for Psychological and Social Factors at Work (QPS Nordic): "Stress means a situation in which a person feels tense, restless, nervous, or anxious, or is unable to sleep at night because his/her mind is troubled all the time. Do you currently feel this kind of stress?'' Five response options are offered: 1: ''not at all,'' 2: ''just a little,'' 3: "to a certain extent,'' 4:''quite a lot,'' and 5: "very much."[145] Exclusion criteria included being younger than 18 or older than 30 years old, having prior formal MM experience, being aerobically trained, or having a condition contraindicating AE. Prior, formal MM experience was defined as receiving formal instruction on and practicing MM within the past year. Aerobically trained status was defined as not participating in weekly quantifiable AE. If the student was in a UNC Lifetime Fitness course, (required health and physical activity class for all UNC undergraduate students) they will still be considered eligible, however partaking in any regular, quantifiable AE beyond the two 50-minute sessions disqualified individuals. Eligible individuals were informed of the study by mental health clinicians at CAPS. Emails sent to and flyers posted in the UNC campus community were

also used for recruitment purposes. Before participation in the study, participants provided written informed consent approved by the Institutional Review Board at UNC. Subjects that did not qualify for the study via criteria 1 were invited to the laboratory to meet with the investigator and determine eligibility by assessing their satisfaction of criteria 2 or 3. Upon confirming eligibility, subjects were randomly assigned (Research Randomizer; randomizer.org) to one of three groups: MM, AE+MM, or Control.

Study Design

Both experimental (MM and AE+MM) groups met for "on-site" administration of their respective protocols three days per week for four weeks. All visits were approximately 40 minutes. Participants also had an "off-site" self-monitored component for their respective group. All MM practice was performed in a seated position in a quiet, dimly lit room.

Group 1: Mindfulness Meditation

Mindfulness Meditation "On-Site" Component

Participants reported to the laboratory three times per week for MM (Day 1, 2, and 3 each week). Each visit lasted 40 minutes. Day 1 had a class-format in which an experienced, qualified MBSR guided the group through a scripted MM session. The script was based on the main tenets of MBSR including "observing," "describing," "acting with awareness," "non-judging of inner experience," and "non-reactivity to inner experience.[6,130] Like MBSR, the session also allowed several minutes for interaction with the instructor including questions and answers, as wellas reflections about the practice. However, it should be noted that the majority of the time was spent on instructor-guided practice as opposed to interactive activities. "On-site" days 2 and 3 consisted of participants reporting to the lab and listening to a 40-minute guided MM track

narrated by Jon-Kabat Zinn - the founder of MBSR.[6] This audio track reviewed the same topics covered on Day 1.

Mindfulness Meditation "Off-Site" Component

Participants were instructed to practice MM with guided audio tracks provided by the researchers. They were instructed to practice by listening to and practicing MM with one audio track lasting at least 20 minutes per day. Eight tracks ranging from 5-40 minutes were provided via MP3 files so as to give the participants several options and avoid monotonousness. Tracks less than 20 minutes were provided to give participants the opportunity to practice for a shorter amount of time if they felt that time was a barrier on a certain day; however, practicing with the 20-minute track was strongly encouraged. The tracks were narrated by Jon Kabatt Zinn and two other professional, experienced mindfulness instructors (one of whom is the Day 1 group-instructor). These tracks contained MM instructions containing the same elements reviewed in the instructor-led Day 1 session and were based on the principles of MBSR.

Group 2: Aerobic Exercise + Mindfulness Meditation

Aerobic Exercise "On Site" Component

Participants reported to the laboratory three times per week for AE performed on a cycle ergometer or treadmill. The session was supervised by a researcher familiar with the study and protocol. Following a 2-3 minute warm-up at a self-selected pace, 20 minutes of AE was performed at or above 40% (intensity) of heart rate reserve (HRR) using the Karvonen formula [(Age-predicted HR_{max} – HR_{rest})(%Intensity)] + HR_{rest}. Next, subjects were allowed a 2-3 minute cool-down at a self-selected pace. A HR monitor (Polar) was used to monitor HR throughout the session and ensure maintenance of at least moderate-intensity AE. Participants were also familiarized with, and reported their rate of perceived exertion (RPE) on the 0-20 Borg scale.

Aerobic Exercise "Off-Site" Component

Participants participated in 60 additional cumulative minutes of AE at a "moderate" intensity (4-6 on the 1-10 Borg RPE scale) to accumulate a net weekly AE duration of 150 minutes.

Mindfulness Meditation "On-Site" Component

The "on-site" MM component for Group 2 was identical to that of Group 1, except that it had a duration of 20 minutes rather than 40. On Day 1, the instructor-led session was 20 minutes and the instructor use the same script used for Group 1. However, the silent periods in-between the verbal instructions were shortened to accommodate the 20-minute duration. On Days 2 and 3 participants in Group 2 listened to a 20-minute track guided by Jon Kabat-Zinn.

Mindfulness Meditation "Off-site" Component

The "off-site" MM component for Group 2 was be identical to that of Group 1, except that they were instructed to practice by listening and practicing MM with one audio track lasting at least 5 minutes per day. The same 8 audio tracks that were provided to Group 1 were provided to Group 2.

Group 3: Control

The Control group did not participate in any intervention.

Daily Journal Log

Participants in Groups 1 and 2 were required to maintain a daily log to report daily compliance with "off-site" requirements of the intervention. Participants in all three groups were also instructed to report any changes in physical activity, diet, sleep, or the occurrence of any major life events. These logs were collected at the end of each of the four weeks.

Dependent Variable Measurement

Demographic information and levels of trait mindfulness were measured prior to the intervention. Prior to, and following weeks 1 and 4 of the intervention, measurements of self-rated psychological and physiological variables were measured. Physiological variables were only assessed in a randomized sub-group (N=5) from each group (prior to dropouts leading to subgroups of N=5, N=4, and N=4 for MM, AE+MM, and Control respectively). Figure 2 illustrates the breakdown of groups and sub-groups prior to dropouts. HR_{rest} was measured both as an outcome measure for these sub-groups as well as a variable used in the calculation of HRR for exercise prescription in Group 2. All physiological variables were measured between the hours of 6-10 AM, following 25-minutes of supine rest in a dimly lit room and having been 12-hours fasted (water was permissible). Subjects in the sub-sample were instructed to refrain from caffeine, alcohol, and vigorous exercise for 12 hours prior to measurements of physiological variables. Dependent variables are listed and described in Table 1.

Perceived Stress

The 10-item modified Perceived Stress Scale[146] questionnaire was used to measure perceived stress. This is the short-version for the original 14-item scale and has been shown to be reliable (Cronbach alpha = 0.78) and equivalent validity in an American probability sample.[146,162]

Depressive and Anxiety Symptoms

The 21-item Depressive Anxiety Stress Scales[147,148] questionnaire was used to measure depressive and anxiety symptoms, which has also been shown to be reliable (Cronbach's alpha0.83-0.90) and valid in young adults.[147, 148]

Dependent Variable	Outcome Level	Instrument/Method	System
Perceived Stress	Primary	Perceived Stress Questionnaire[146]	Psychological
Depression and Anxiety	Primary	Dimensional Anxiety Stress Scales[166]	Psychological
Resting Heart Rate*	Secondary	HR Monitor	Autonomic
Heart Rate Variability*	Secondary	Electrocardiogram, (RMSSD)	Autonomic
Peripheral Blood Pressure*	Secondary	Oscillometric Cuff	Autonomic
Aortic Stiffness*	Secondary	Pulse Wave Velocity	Vascular

Table 1. Characteristics of dependent variables. *RMSSD, Root mean squared of standard deviation of R-R intervals; *Only assessed in sub-sample.*

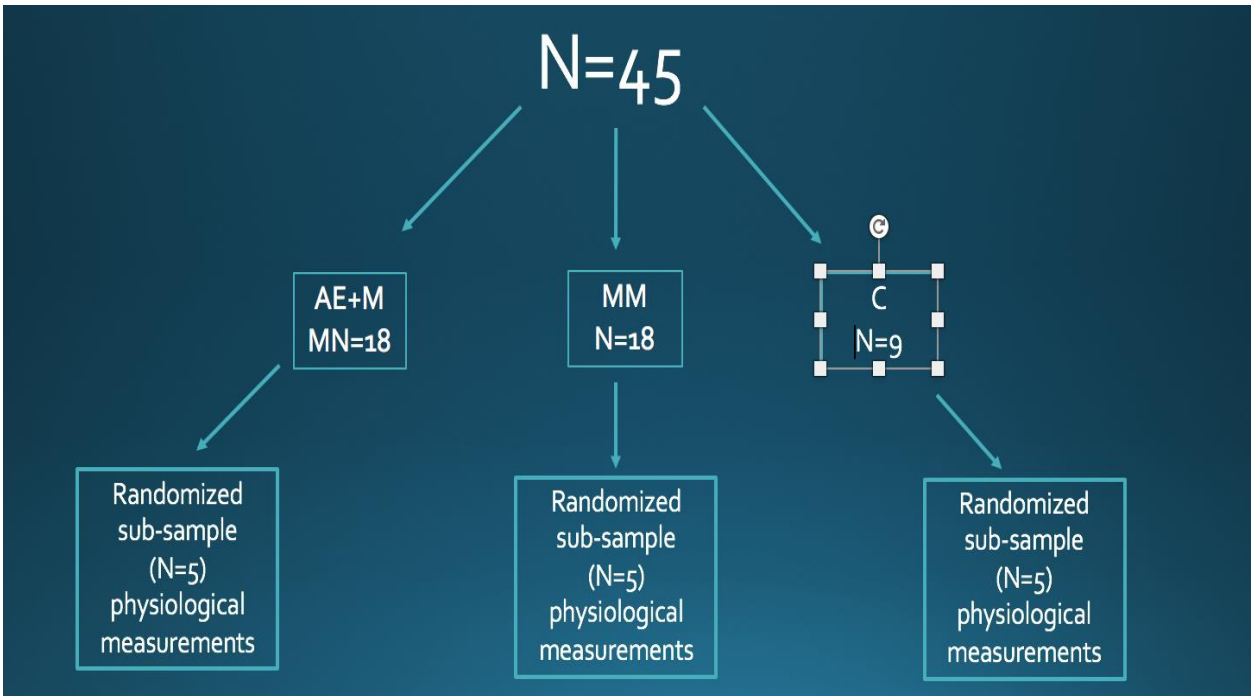

Figure 2. Group and sub-group flow diagram.

Cardiovascular and autonomic measures

Arterial stiffness was measured using applanation tonometry-derived carotid-femoral pulse wave velocity (PWV), (SphygmoCor XCEL). Sub-systolic and systolic brachial occlusions at the upper arm around the upper arm to obtain HR, SBP and DBP were also measured using this device. Heart rate variability [Root mean squared of the standard deviation of R-R intervals (RMSSD)] was measured for 5 minutes using a standard 3-lead electrocardiogram (Lab Chart, ADInstruments).

Statistical Analysis

The alpha and beta levels were set a-priori at 0.05 and 0.80 respectively. G-powered software (Dusseldorf, Germany) was subsequently used to compute a sample size of 39. Baseline demographics and anthropometrics were measured and are reported as means ± SD. Significance was denoted as $p < 0.05$. A repeated measures 3x2 analysis of variance was used to assess main effects of group placement and time. An a-posteriori natural log transformation was performed on the psychological data points, and an additional analysis of variance was performed. Cohen's d effect sizes of pre to post changes in PSS and DASS were also calculated. Statistics were performed using Statistical analyses were performed using SPSS Statistical Software Version 21.0 (IBM, Chicago, Il)

CHAPTER IV: RESULTS

Participant characteristics are shown in **Table 2.** Participant psychiatric medication use, intervention compliance, and dispositional (trait) mindfulness are shown in **Table 3.**

Group	n	Age (yrs)	Height (m)	Weight (kg)	BMI (kg/m^2)
MM	10 (9 F)	20.09 ± 2.79	1.69 ± 0.04	68.38 ± 16.4	24.02 ± 5.27
AE+MM	16 (14 F)	20.91 ± 2.91	1.65 ± 0.1	62.02 ± 9.33	22.64 ± 2.83
Control	6 (4 F)	20.06 ± 0.95	1.69 ± 0.11	76.67 ± 16.45	27.28 ± 6.8
Total	32	20.49 ± 2.65	1.67 ± 0.09	66.75 ± 14.45	23.94 ± 5.01

Table 2. Participant characteristics.

Group	Trait Mindfulness	Psychological = Rx	% Compliance
MM	112.4 ± 14.9	n=2 (20%)	87 ± 0.1
AE + MM	107.88 ± 13.1	n=5 (31%)	92 ± 0.08
Control	111.67 ± 15.94	n=3 (50%)	N/A
Total	110 ± 15.69	n=10 (31)	90 ± 0.09

Table 3. Participant trait mindfulness, psychiatric medication, and intervention compliance. *Rx, Psychiatric medication; Trait, dispositional*.

Psychological Measures

Perceived Stress

There was no group x time interaction (p=0.12). There was a main effect of time where PSS at Base (p<0.001) and at Wk1 (p=0.04) was significantly higher compared to at Post (Base: 23.67 ± 0.91; 1Wk: 21.49 ± 1.24; Post: 18.19 ± 0.96). There was no main effect of group (p=0.49). Cohen's d effect sizes of the pre to post changes in PSS were -1.33, -1.24, and -0.45 for the MM, AE+MM, and Control groups respectively. PSS and DASS scores by group and across time are shown in **Table 4**.

Depression and Anxiety

There was no group x time interaction (p=0.21). There was a main effect of time where DASS at Base (p=0.004) and at Wk1 (p=0.01) was significantly higher compared to at Post (Pre: 24.97 ± 2.13; 1Wk: 21.5 ± 1.66; Post: 17.49 ± 1.40). There was no main effect of group (p=0.70). The Cohen's d effect sizes of the pre to post changes in DASS were -1.03, -0.97, and

Group/Measure		Baseline	1Wk	Post
MM	PSS	24.70 ± 5.86	24.1 ± 7.99	18.10 ± 3.87
	DASS	26.20 ± 13.21	22.3 ± 11.54	15.0 ± 7.97
AE+MM	PSS	23.81 ± 5.81	20.69 ± 7.80	15.81 ± 7.01
	DASS	25.2 ± 11.95	19.53 ± 9.69	15.13 ± 8.62
Control	PSS	22.50 ± 4.55	19.67 ± 3.96	20.67 ± 3.34
	DASS	23.50 ± 11.04	22.67 ± 5.45	22.33 ± 6.55

Table 4. Psychological Measures (Non-transformed) across Group and Time

-0.13 for both the MM, AE+MM, and Control groups respectively. Results for both the PSS and DSS included three interpolated means for the Control group at Wk1 and Post time-points to account for dropouts.

Physiological Measures

Resting Heart Rate

There was no group x time interaction (p=0.50). There was a main effect of group for resting HR, where the AE+MM group had a significantly lower resting HR than Control (AE+MM: 53.43 ± 3.73 bpm; Control: 70.42 ± 4.31 bpm, p=0.01). There was no main effect of time (p=0.67).

Systolic Blood Pressure

There was no group x time interaction (p=0.90). There were no main effects of time (p=0.45) or group (0.31) for SBP.

Diastolic Blood Pressure

There was no group x time interaction (p=0.16). There was a main effect of group where the MM group had a significantly higher DBP than the AE+MM group (MM: 72.75 ± 1.96 mmHg; AE+MM: 60.94 ± 2.19 mmHg, p=0.01). There was no main effect of time (p=0.62).

Arterial Stiffness (Pulse Wave Velocity)

There was no group x time interaction (p=0.09). There were no main effects of time (p=0.17) or group (p=0.11).

Heart Rate Variability

There was no group x time interaction (p=0.53). There were no main effects of time (p=0.73) or group (p=0.06).

Post-Hoc Analyses

Following the analysis of the initial statistical procedures, which were determined *a-priori*, the PSS and DASS scores were transformed using a natural logarithm. Importantly, this was not planned in the *a-priori* analysis schema. However, this subsequent analysis was performed in an attempt to deal with the large variance due to participant attrition and an under-powered sample size. Performing a natural log transformation on the PSS and DASS scores resulted in group x time interactions for PSS and DASS that more closely approached statistical significance (PSS: p = 0.09; DASS: p = 0.07).

As can be seen more clearly by the absolute means in **Table 4**, **Figure 3**, and **Figure 4**, this trend was characterized by marked reductions in PSS and DASS scores (from Pre to Post) occurring within the AE+MM group (PSS: 34%: DASS: 40%)and MM group (PSS: 27%; DASS: 43%). A seemingly negligible decrease occurred within the Control group [PSS: 8% (p=1.00); DASS: 4% (p=1.00)].

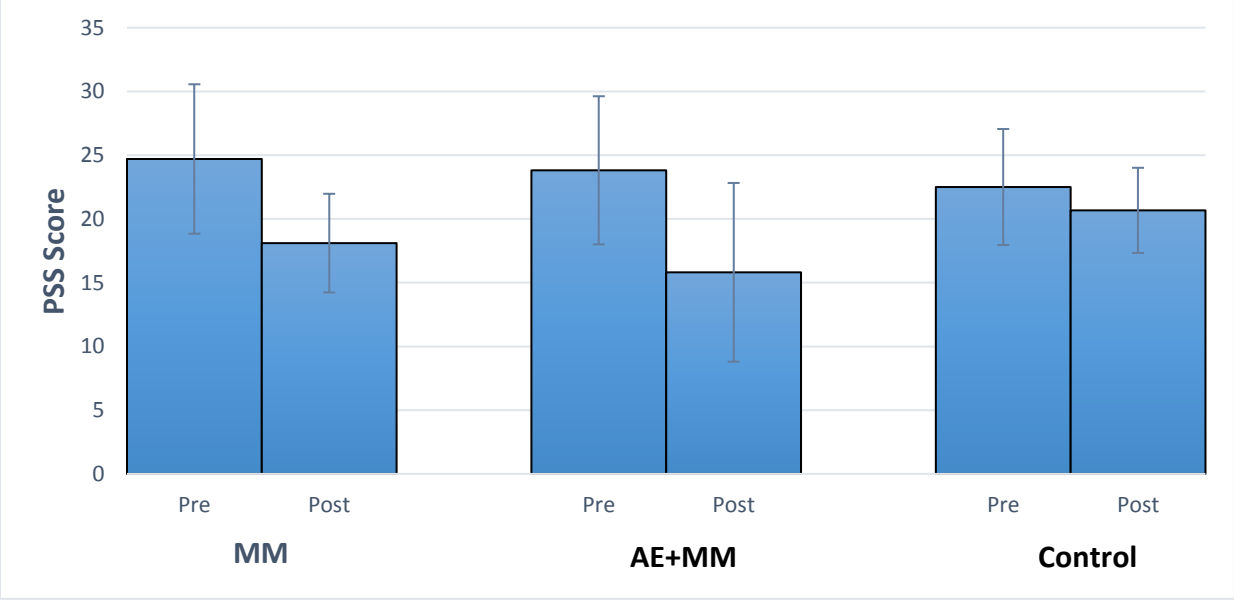

Figure 3. Perceived Stress Scale Scores at Pre- and Post-intervention by group.
AE, Aerobic Exercise; MM, Mindfulness Meditation; PSS, Perceived Stress Scale.

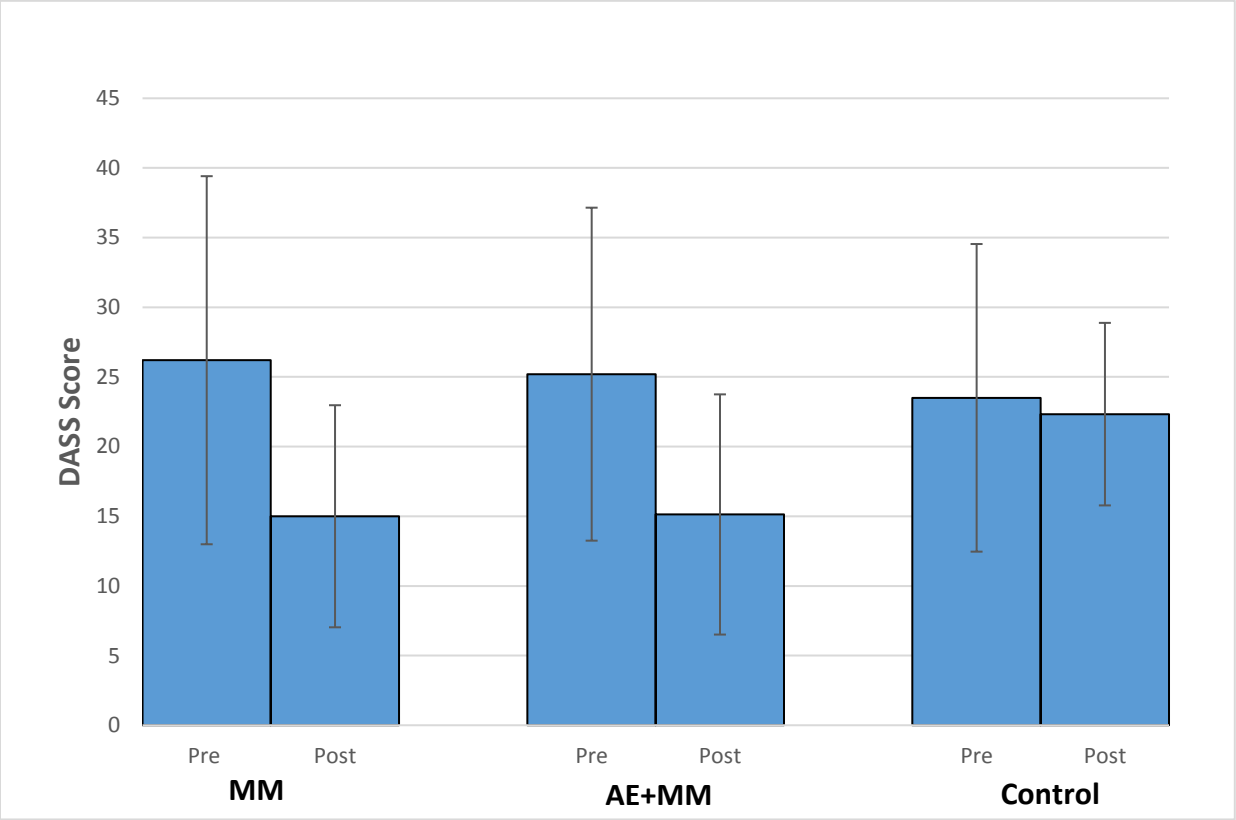

Figure 4. Depression Anxiety Stress Scales Scores at Pre- and Post-intervention by Group.
AE, Aerobic Exercise; MM, Mindfulness Meditation; DASS, Depression Anxiety Stress Scales.

CHAPTER V: DISCUSSION

The current study assessed the integrative stress-reducing effect of AE + MM versus MM alone on stress and stress-related in symptoms in college students experiencing high levels of psychological distress. Though the current study did not result in any statistically significant findings, the data does suggest that the experimental interventions did reduce psychological measures of stress, anxiety, and depression. Simply, doing *something* seemed to be better than doing nothing. Notable reductions in PSS and DASS scores - the primary outcomes of the current study – occurred in both the MM group (PSS: 27%; DASS: 43%) and AE+MM group (PSS: 34%; DASS: 40%), while a relatively minimal decrease occurred within the Control group (PSS: 8%; DASS: 4%).

It was hypothesized that there would be an additive beneficial effect of AE and MM, as compared to the effects of MM alone, on stress-related psychophysiological parameters in college students experiencing high levels of psychological stress. This hypothesis was not supported in the present study due to both the lack of statistical significance as well as the largely similar effects that MM and AE+MM had on stress, anxiety, and depression.

Aerobic Exercise, Mindfulness Meditation, and Psychological Measures

The stress-reducing and anti-depressant effects of moderate-intensity AE have been established previously in human studies as well as animal models [120,149,10150]. Thus, it can be reasonably assumed that the AE component of the AE+MM intervention contributed in part to the improvements observed in this group. Similarly, mindfulness-based interventions (MBI's), which typically employ some degree of exercise or physical activity in conjunction with MM,

have been shown to decrease maladaptive psychological symptoms of stress[151,113,132] Thus, our findings seem to be in agreement with previous research in that both experimental groups seemed to improve psychological measures.

A study by Goldin et al. showed that while AE and MM interventions both decreased emotional reactivity, only the MM intervention improved emotional regulation in individuals with generalized social anxiety disorder[132]. Another study by Prakhinkit et al. demonstrated that mindful walking was found to decrease depressive symptoms compared to traditional walking in a depressed elderly cohort[152]. However, the former study only specified AE frequency and not intensity or duration, while the latter study's use of walking may not have induced an intensity high enough to promote beneficial psychological effects[111].

On the other hand, the current study *did* ensure accurate reporting of AE frequency, intensity, and duration with findings suggesting largely similar psychological effects of moderate-intensity AE and MM occurred. Baghurst et al. also showed that an integrative stress-management intervention consisting of both exercise and cognitive-behavioral psychological components (which could be loosely compared to our AE+MM group), was similarly effective in improving psychological outcomes as a group that focused purely on physical activity participation in among college students[153]. Clearly, additional methodologically sound research is needed to better assess the differential and potentially synergistic stress-reducing capacities of AE and MM, yet it does seem evident that both AE, if performed at a high-enough relative intensity, and MM both effectively contribute to reductions in stress and improvements in psychological health.

Aerobic Exercise, Mindfulness Meditation, and Physiological Measures

Only a randomized sub-sample of five participants per group completed physiological assessments. Two drop-outs in this sub-sample reduced the total to 13, making it difficult to interpret our physiological results (i.e., being underpowered). No group x time interactions were found, and it is unknown if a larger sample size would or would not result in any statistically or physiologically meaningful effects.

Nevertheless, evidence does exist showing improvements (both at rest and in response to an acute stressor) in stress-related physiological measures following AE and MM interventions[10,11]. The beneficial effects of AE on BP, HRV, and sub-clinical markers such as HR and arterial stiffness are well known, which is largely attributed to modulations in autonomic function.[124,125,127,154] Fewer studies have sought to examine the physiological effects of MM. Similar to AE, MM may result in improvements in BP[155], HRV[138], and cortisol[156], however results are mixed[157,136]. While the minimal physiological data limited our ability to assess the physiological effects of our intervention, additional studies are warranted to assess (1) the individual effects of MM and AE, (2) if there is a differential type and/or size of effect of AE versus MM, and (3) if there is a synergistic effect of AE and MM on such measures when combined.

Limitations

The primary limitation in this study was the underpowered sample size. Our power calculation indicated a sample size of 39 individuals, prompting recruitment of 48 individuals in anticipation of attrition. However, only 32 participants completed the study. Of the 16 participants that gave consent but did not complete the study, nine had been randomized to the MM group, two were in the AE+MM group, three were in the control group, while one had

fallen into exclusion criteria prior to randomization. Interestingly, seven of the 13 individuals that did not complete the study dropped out *before* the intervention commenced (due to concern about the time commitment) while six participants dropped out during the intervention. Of the six that dropped out during the study, three were in the control group and simply failed to complete the post-intervention testing, while two were in the MM group and one was in the AE+MM group. Based on the higher attrition among the non-AE groups (both before and after the commencement of the intervention), it may be that the AE component of the AE+MM intervention provided a more tangible, observable, or expected "beneficial" effect, and encouraged intervention participation and compliance. Thus, while the 29% attrition rate may seem to indicate poor feasibility, in reality only 8% (n=3) of the initial 18 individuals in the experimental groups dropped out *during* the study. In other words, though attrition did limit our ability to reach statistical significance, it was not necessarily an indicator of feasibility. Moreover, the intervention groups were approximately 90% compliant in adhering to the 800-minute intervention, further indicating the feasibility of the intervention strategy.

Another limitation was our reliance on self-reporting for the assessment of psychological variables as well as tracking "off-site" compliance. However, subjective questionnaires and participant logs are commonly used to assess psychological measures[158] and home-based study compliance[159] respectively.

Lastly, the high ratio of females to males (84% F) in the current study makes the findings difficult to generalize to males. However, it must also be pointed out that females have higher prevalence of depression, report higher levels of stress and physical symptoms associated with stress compared to males, and are more likely to seek out stress-management strategies and general health care than their male counterparts[160,161]. Thus, while the current sample was

skewed in terms of gender, it may partially reflect the true population of high-stress young adults in a university setting. This information may also be useful in highlighting the need to better promote mental health-seeking behavior in males.

Considerations and Implications

While it seems clear that both MM and AE+MM were effective at reducing stress and psychological symptoms of stress and anxiety, it is difficult to elucidate if and how these interventions induce differential effects on these psychological measures. However, closer examination of the data reveals an intriguing possible phenomenon. While not supported by statistical significance, the AE+MM intervention resulted in greater reductions in perceived stress (compared to MM), whereas the MM intervention resulted in greater reductions in symptoms of depression and anxiety (compared to AE+MM). Thus it could be speculated that while AE may strongly influence symptoms of general stress (possibly via increased self-efficacy, neurological adaptations, and stress-pathway regulation)[10], MM may be superior in targeting specific clinical components of psychiatric illness (via incorporation of new cognitive-behavioral strategies which are fundamental aspects of the practice). [134,109]

This relationship continues to hold up when assessing the clinical significance of these psychological improvements. While there are no established clinical cut-offs for the PSS, a poll of 2,387 respondents in the US found the average PSS score among 18-29 year olds to be 14.2.[162] In the current study nine of the 26 (35%) participants within the two intervention groups had a baseline stress score above this population mean, yet finished with a post-intervention PSS score below this value. Seven of these participants were in the AE+MM group (44% of group), while two were in the MM group (20% of group). Thus, a greater number and percentage of

participants within the AE+MM group versus the MM group began the study higher than the mean population score and concluded the study at a lower score.

Similar to the PSS, there are no established clinical cut-off values for the DASS measure. However, mean values have been compiled among various clinical populations.[163] Six of the 26 (23%) participants within the intervention groups had baseline DASS scores above the reported average score (31) of persons clinically diagnosed with a specific phobia anxiety disorder, yet finished the intervention with a score below this level. Three of these participants were in the MM group (30% of group), while three were in the AE+MM group (19% of group). In contrast to PSS, the greater percentage of participants within the MM group as opposed to the AE+MM group experiencing a clinically significant improvement in DASS scores gives credence to the possibility that AE may be a more robust regulator of general stress, while MM may be a more robust regulator of possibly more severe clinically significant psychiatric symptomology.

Several studies[132,152,153], but not all[164], have been in agreement with this hypothesis in that they demonstrated superior anti-depressant and anti-anxiety capacities of MBI's (including those that both include and exclude exercise activities) than interventions solely employing exercise, although again these studies are limited by sub-optimal descriptions of exercise variables. Though hypothetical at present, if confirmed through future research, scientists and clinicians could better formulate interventions for specific populations depending on levels and type of psychological stress. To better examine this potential phenomenon, future research should compare stress-, depression- and anxiety-reducing effects of a methodologically sound AE intervention with a MM and/or AE+MM intervention.

Another consideration is attempting to determine whether specific sub-sets of a "high-stress" population are more or less like likely to benefit from AE, MM, or AE+MM depending

on several baseline characteristics of individuals. For example, it has been suggested that high levels of dispositional (trait) mindfulness may moderate the effect of stressors, which in turn, could be argued to effect the efficacy of an MBI[135,165]. However, our results did not appear to show any relationship between dispositional mindfulness and efficacy of intervention. Other baseline characteristic at baseline to consider are the use of psychiatric medication. Again, no relationship in medication use or baseline stress appeared to be associated with the efficacy of intervention. Future studies should continue to assess these potential moderators, as it has been scarcely examined in stress-reduction research.

A final topic, highlighted in the current study, that future research should address is the feasibility, attrition and compliance of AE and MM interventions. While compliance was surprisingly high in both of the intervention groups among participants that began the study, it is interesting to note that of the 18 individuals assigned to the AE+MM, only three participants in the AE+MM group dropped out (two dropped before the study started, and one dropped after the first week). In contrast, of the 18 individuals that were assigned to the MM group, there were 9 dropouts (6 dropped before the study started, and two dropped after week 1). Thus, it may be the case that AE alone, or combining AE+MM may be more "attractive" than MM alone (due to increased self-efficacy and greater perception of tangible benefits) and thus increase feasibility and compliance while reducing attrition in this young population.

Conclusion

This appears to be the first study to directly compare the stress-reducing effects of an integrative AE+MM intervention with a MM intervention. Neither AE+MM nor MM interventions resulted in significant changes in perceived stress, anxiety, or depression, which

were the primary outcomes in this study. Participant attrition and high inter-individual variability likely limited our ability to find significance.

Nevertheless, both intervention groups exhibited substantial improvements in psychological outcomes, whereas no changes occurred in the control group. Despite the lack of clinical significance, these findings suggest that doing *something* is better than doing nothing, and provides further evidence that MBI's are effective in reducing psychological symptoms related to stress, anxiety, and depression. Future research should seek to compare AE with an AE+MM and/or MM intervention to continue to assess differential effects of each activity on stress and related variables. A particular emphasis should be placed on ensuring appropriate intensity and reporting of AE, recruiting an adequate sample size, and assessing stress-related physiological measures.

In conclusion, while additional research is needed to better understand the potential differential and synergistic psychophysiological effects of AE and MM, the current study does suggest that interventions comprising these components are feasible may improve stress and related symptoms in young adults.

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