

Physical Activity and Depressive Symptoms during the COVID-19 Stay at Home Order in North
Carolina

Madison Gill
North Carolina Wesleyan College

Abstract

BACKGROUND: Studies show that rates of depression have increased during the Corona Virus Disease of 2019 (COVID-19) pandemic, and that this may be due, in part, to increased levels of chronic stress and social isolation. Physical activity (PA) has been shown to help prevent the development of depression, and public health messaging during the COVID-19 pandemic has consistently highlighted the importance of staying physically active. How COVID-19 restrictions have impacted PA participation is currently unknown. This study aimed to explore PA participation, and the relationship between PA and depressive symptoms, in North Carolina (NC) residents during the April, 2020 NC stay at home order.

METHODS: Participants (n=193, mean age: 35.6y +/- 14.0) were recruited from 29 counties in NC during the COVID-19 stay at home order. Participants were asked to complete an online survey about depressive symptoms (Beck Depression Inventory), access to PA activities, PA activity over the last month (5-point likert scale ranging from “much lower” to “much higher” than usual), and average weekly PA participation (International Physical Activity Questionnaire). Total min/week of PA was calculated from the IPAQ, and PA activity likert scale results were dichotomized as (1) lower than usual or (2) the same/higher than usual.

RESULTS: Forty-four percent of participants reported that their PA levels were lower than usual during the NC stay at home order. Individuals who reported that their PA levels were lower than usual reported significantly lower durations of weekly PA than those who reported that their PA levels were the same or higher (320.3 min/week vs. 538.7min/week; $t = -4.01$; $p < 0.001$). Regression analysis revealed that, after controlling for age, sex, BMI,

education, race, marital status, and income, lower total PA duration per week significantly predicted higher depressive symptoms ($\beta = -0.19$, $p < 0.008$).

CONCLUSIONS: A substantial proportion of individuals reported lower than usual PA during the NC stay at home order, which was associated with significantly reduced weekly PA durations. Consequently, lower weekly PA was associated with higher depressive symptoms.

These findings should be considered preliminary, considering the small sample size and use of self-report measures, but they suggest that future study of the unique barriers and facilitators of PA participation during the COVID-19 pandemic is warranted, particularly with regards to mental health outcomes.

Introduction

At the end of March 2020, North Carolina (NC) declared a statewide stay at home order, in response to the 2019 novel coronavirus (COVID-19), an unprecedented pandemic that affected individuals across the world. As part of the NC stay at home order, and in an attempt to slow the spread of COVID-19, many businesses, restaurants, fitness facilities, and schools were closed (Cooper, 2020). In addition, individuals were told to remain at home other than for essential travel to get supplies, groceries, etc. Visitor restrictions at hospitals, clinics, and assisted living facilities were imposed, and social distancing measures were put in place. As a consequence of high levels of social isolation, rates of depression and anxiety increased (Robb et al., 2020; Sepulveda-Loyola, 2020; see also figure 1). There is strong evidence to suggest that chronic stress is one of the most influential risk factors for the development of mental health disorders, including depression (Sanders, 2014). Considering that the COVID-19 pandemic has likely greatly increased levels of chronic stress, it is perhaps not surprising that the prevalence of depressive disorders increased during this time (Newby et al., 2020).

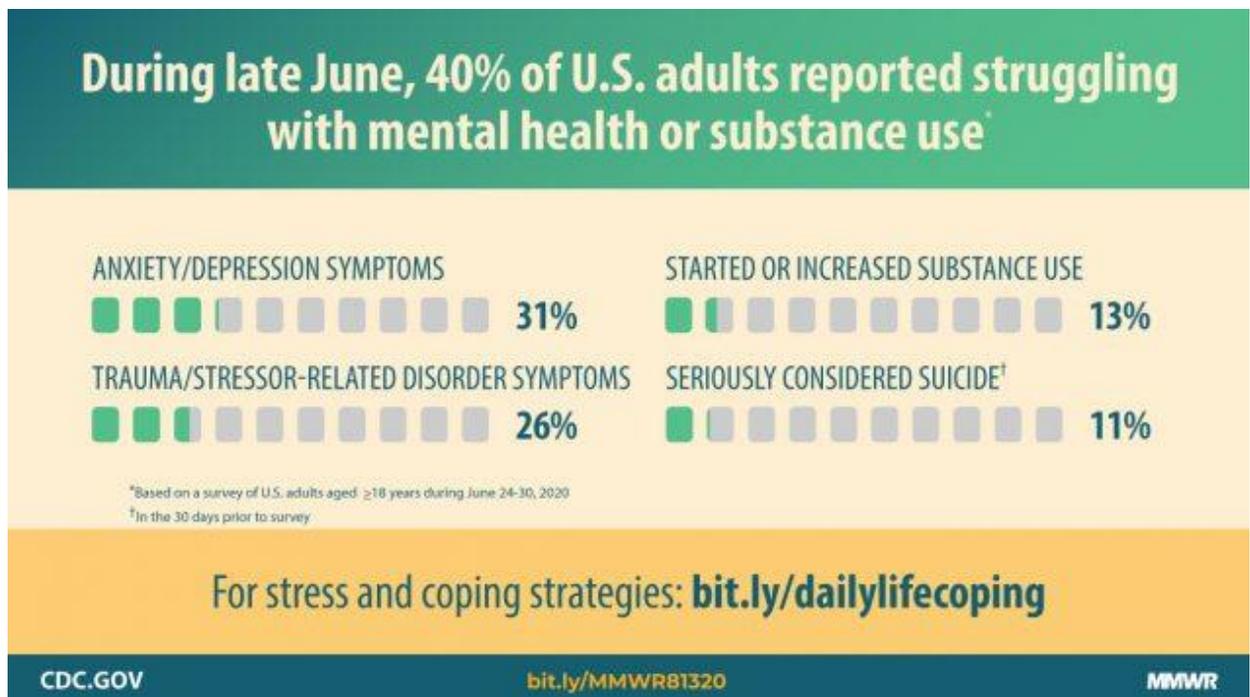


Figure 1: Czeisler, M. É., Lane, R.I., MA, Petrosky, Emiko, MD, Et Al. (2020). Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic – United States, June 24-30, 2020. *CDC Weekly*, 69(32);1049-1057. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6932a1.htm>

A 2020 study, released in February 2021 shows the longitudinal impact of mental health prior to COVID-19 and since the virus began its violent spread in early 2020 (Pan et al., 2021).

Physical activity (PA) has shown to have many health benefits, including a major role in reducing depression risk (Ligouri et al.,2021). This could be due, in part, to the impact of regular PA on stress processing. Several studies suggest that regular PA may improve the physiological and behavioral response to stress (Jayasinghe et al., 2017; Klaperski et al., 2014; Nigdelis et al., 2018; Nguyen-Michel et al., 2006), and that high cardiorespiratory fitness (CRF) may help improve stress regulation (Crowley et al., 2015; Crowley et al., 2020).

The restrictions associated with the COVID-19 pandemic have created many barriers to PA participation. For example, a study by Ng et al. (2020) suggests that school closures may

have contributed to reduced PA participation in children and adolescents. The Centers for Disease Control and Prevention (CDC) has also reported some barriers unique to COVID-19, which included gym closures, lack of energy, and certain weather conditions which may have prevented individuals from accessing outdoor PA resources (CDC, 2020). The precise impact of COVID-19 restrictions on PA behavior is not currently known, but considering these reports of unique and increased barriers to PA during the COVID-19 restrictions, it is likely that PA behavior has been negatively impacted by COVID-19.

Importantly, studies have shown that both regular PA, and high CRF may help to prevent the development of depression (Crowley et al., 2015; Harvey et al., 2018; Kandola et al., 2019; Sui et al., 2009). Other studies have shown that high CRF may also be protective against the development of depressive symptoms in stressful situations (Becofsky et al., 2015; Crowley et al., 2015). Whether PA is associated with a reduced risk for the development of depression during the COVID-19 pandemic is not currently known. This study, therefore, aimed to explore the association between PA participation and depressive symptoms during the April, 2020 COVID-19 Stay at Home order in NC. Considering the impact of the COVID-19 restrictions on PA behavior, we also sought to explore: (1) changes in PA participation; (2) self-reported PA behavior; and (3) PA resources accessed, during the April, 2020 COVID-19 NC Stay at Home Order.

Review of the Literature

Chronic Stress and Depression Risk

Several chronic stress-related mechanisms have been suggested to play a pathophysiological role in the development of depression. These include hypothalamic pituitary adrenal axis (HPA axis) dysregulation (Crowley et al., 2020), altered brain monoamine

(dopamine, norepinephrine, serotonin) availability (Delgado, 2000), and altered brain structure and function (Leuchter et al., 1997).

Hypothalamic Pituitary Adrenal Axis (HPA axis) Dysregulation

The HPA-axis is a part of the neurohormone system which assists in managing the body during stress (Dunlavey, 2018). The HPA axis is one of the body's main stress response pathways (Alschuler, 2017). Stress induces the release of corticotrophin releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus (Alschuler, 2017). CRF is a hormone that stimulates the anterior pituitary gland to release adrenocortotropic hormone (ACTH; Alschuler, 2017). Next, ACTH activates receptors on the adrenal cortex to release cortisol (Alschuler, 2017). During an acute stressor, peak cortisol release can take minutes to hours following the stressor (Alschuler, 2017). When cortisol levels reach their peak, termination of the HPA axis response to stress begins via negative feedback regulation, returning the body to homeostasis (see figure 2 below; Alschuler, 2017 ; Chrousos, 2009).

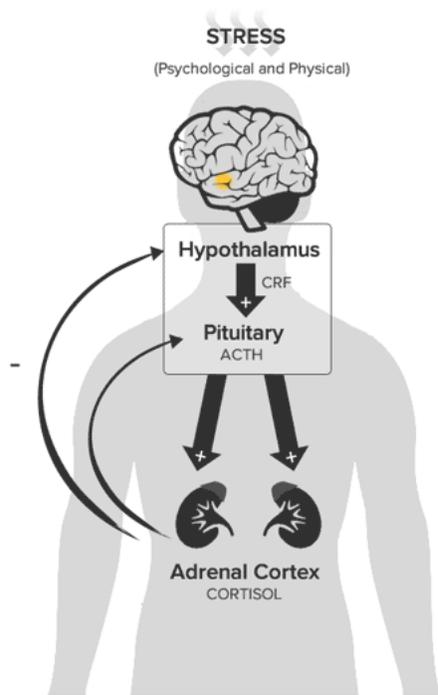


Figure 2: Alschuler, L. (October 31, 2016). The HPA Axis. *Integrative Therapeutics*.

<https://www.integrativepro.com/Resources/Integrative-Blog/2016/The-HPA-Axis>

Cortisol plays a critical role in regulating cardiovascular, metabolic, and immunologic changes during acute stress. For example, increased circulating cortisol in response to acute stress promotes increased blood and brain glucose levels, a mechanism intended to supply the body with energy during a fight or flight situation (Thau, et al., 2020). Cortisol may also act as an immunosuppressant, and high levels of circulating cortisol during acute stress have been shown to down regulate the immune system (Herbert, 2012). Additionally, the release of cortisol in response to acute stress plays a role in the hemodynamic stress response (by helping to increase heart rate and blood pressure during acute stress) (Whitworth et al., 2005). These physiological processes are appropriate in the context of acute stress, however, when cortisol levels remain chronically elevated (a common finding in individuals with depression), negative

health effects can occur. For example, chronically elevated cortisol levels can depress the immune system (increasing risk of illness and infection), increase risk for cardiovascular diseases (such as hypertension), and increase risk for other diseases such as type II diabetes and certain cancers (Alen et al., 2018; Chrousos, 2009).

Dysregulation of HPA axis functioning (most commonly measured by peripherally circulating cortisol levels) is a common finding in individuals with depression (Yokoyama et al., 2015). Moreover, it has been suggested that dysregulation in HPA axis functioning is a major factor in the development and maintenance of depressive disorders (Crowley et al., 2014). For example, multiple meta-analyses of the association between basal and stress-induced cortisol and depression have consistently shown that individuals with depression exhibit altered (blunted or elevated) basal cortisol levels and altered (blunted or exaggerated) cortisol levels during acute stressors. These findings further support the hypothesis that the HPA axis may be dysregulated in individuals with depression (Burke et al., 2005; Stetler et al., 2011; Zorn et al., 2017).

Altered Brain Monoamine Availability

The monoamine hypothesis of depression states that depression can occur when levels of serotonin, norepinephrine, or dopamine are altered (Delgado, 2000). In this manner, there are either not enough monoamines (serotonin, norepinephrine, and dopamine) produced, or the receptors of these monoamines are inactive or altered, negatively impacting monoamine availability. Serotonin is involved in several processes in the body, including regulation of the sleep-wake cycle, metabolism, and emotion regulation (Bancos, 2018). Low serotonin availability has been linked to depression (Bancos, 2018), and considering the role of this monoamine, low serotonin availability may, in part, explain some symptoms that are associated with depression including changes in appetite, increased anxiety, and digestive issues. Dopamine

assists in the regulation of many bodily functions, such as sleep and metabolism (Vandergreindt, 2020). Dopamine is the chemical that plays a large role in motivating an individual and is largely responsible for the joy that comes to the individual when a goal is met or a task is completed (Vandergreindt, 2020). A few of the main symptoms of depression are low motivation depressed mood, and a loss of interest in things that were once enjoyed (Vandergreindt, 2020). Research suggests that these symptoms may be, in part, caused by dopamine dysfunction (Vandergreindt, 2020). Norepinephrine is a form of adrenaline that the body uses to help regulate the stress response (Zoppi, 2019). Norepinephrine is also a neurotransmitter in the central nervous system that affects attention span and action (Zoppi, 2019). The fight or flight response is also controlled by norepinephrine, which can increase the heart rate, release glucose, and increase blood flow to muscles (Zoppi, 2019). Norepinephrine activates the amygdala, which in turn produces the fearful behavior, but can also enhance long-term storage of negative, stressful memories. (Zoppi, 2019). Dysregulation in norepinephrine signaling has been suggested as a pathophysiological mechanism in the development and maintenance of depression.

How chronic stress influences monoamine availability is not entirely understood; however, it has been proposed that chronic stress may induce repetitive and/or prolonged stimulation of monoaminergic neurons, resulting in long-lasting imbalances in central nervous system neurotransmitter functioning (Flugge et al., 2004). Consequently, changes in brain monoamine availability caused by chronic stress are suspected to contribute to the development of depression (Boku et al., 2018). In addition, studies have shown that chronically elevated cortisol levels may lower serotonin availability, further suggesting a link between chronic stress and monoamine availability in the development of depression (Tafet et al., 2001).

Altered Brain Structure and Function

There have been many studies completed that have found that regions of the brain may be altered in patients diagnosed with major depressive disorders (Zhang et al., 2018). Regions of the brain that have been shown to be altered in individuals with depression include the cerebral cortex, hippocampus, thalamus, and the amygdala (Miller, 2019; McEwen).

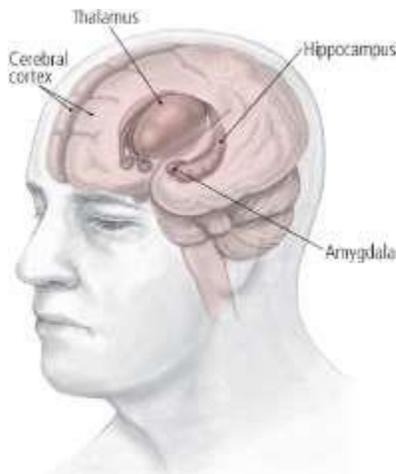


Figure 3: Miller, C. M. (June 24, 2019). Onset of depression more complex than a brain chemical imbalance. *What causes depression?*

<http://www.health.harvard.edu/newsweek/what-causes-depression.htm>.

Alterations in structure and function of these brain regions is important in the context of depression due to the roles these brain regions play. For example, the prefrontal cortex is responsible for complex cognitive behavior, personality expression, decision making, and handling social behavior (Dahlitz, 2017). In MDD, deficits in pre-frontal cortex functioning have been associated with cognitive dysfunction, increased negative emotions or behaviors, and suicidal behaviors or acting upon suicidal thoughts (Pandya, 2012).

The amygdala is essential in emotion regulation, and amygdalar volume has been found to be reduced in individuals with depression (Pandya, 2012). For example, a recent study by Hao

He et al (2017) found that magnetic resonance imaging (MRI) scans of individuals with MDD showed lower gray matter in the amygdala and cerebellum, compared to healthy controls. Because emotion is regulated by the amygdala and cerebellum, this highlights a brain basis for the observed symptoms in individuals with MDD. In addition, the amygdala has also been associated with the “fear response” in humans (Ressler, 2010). Consequently, individuals that have been diagnosed with post-traumatic stress disorder (PTSD) have been found to have a more active amygdala, and this appears to also be the case for individuals with MDD who have higher levels of anxious-type symptoms (Ressler, 2010).

The hippocampus, which plays a major role in learning and memory, has been shown to be negatively affected by both chronic stress and depression. In fact, reduced hippocampal volume is one of the most consistent neurological findings in individuals with depression (Frodl et al., 2006; Lange et al., 2004; Neumeister et al., 2005; Videbech et al., 2004). Reduced hippocampal volume may be, in part, responsible for cognitive symptoms of depression such as motivation, and attention and memory impairments (Frodl et al., 2006).

Finally, the thalamus (which assists in relaying sensory and motor signals to contribute to one’s consciousness and alertness) has been shown to be negatively impacted in individuals with depression (Pandya, 2012; Torrico et al., 2020). It is thought that impairments in thalamic functioning in individuals with depression may help to explain cognitive impairment which often accompanies depression (Kang et al., 2018).

Allostatic Load and Depression Risk

To understand why chronic stress is associated with these biological alterations in the body, which increase the risk for the development of depression, it is important to understand the role of chronic stress in allostatic load.

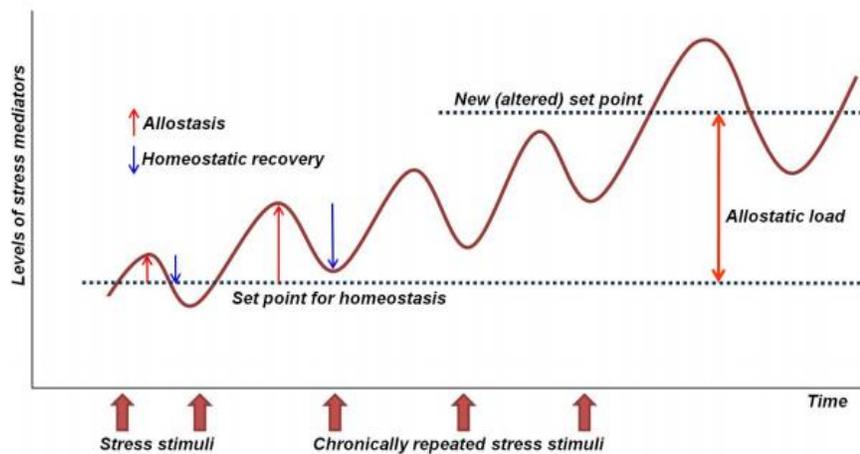


Figure 4: Taken from Lee, D. Y., Kim, E., & Choi, M. H. (2015). Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. *BMB reports*, 48(4), 209–216. <https://doi.org/10.5483/bmbrep.2015.48.4.275>

As shown in figure 4 above, when the human body is exposed to a stressful stimulus, biological processes (neurotransmitter release, hormone regulation, inflammatory responses, etc.) in the body respond in order to allow the body to appropriately react to the stressful stimuli and then return to homeostasis (Lee et al., 2015). This is known as adaptation (Lee et al., 2015). In some individuals, when presented with chronic stress (whether extended over a period of time, or repeated stressors), the body fails to adequately respond and/or recover from stressful stimuli, and the set point for homeostasis can be shifted (Lee et al., 2015). This shift may result in the body being chronically exposed to higher levels of stress-related factors (stress hormones, inflammatory cytokines, etc.), which can increase risk for disease, including mental health disorders (McEwen, 2003).

Social Isolation and Depression Risk

Social isolation is defined as the absence of contact with others and lack of engagement with the community on a day after day basis (Tiwari et al., 2012). The COVID-19 pandemic has

greatly increased social isolation among individuals, and studies suggest this may be one mechanism underlying the impact of the COVID-19 pandemic on depression risk (Pietrabissa et al., 2020; Webb, 2020). Indeed, both epidemiological and experimental research suggests that social isolation is strongly linked to increased depression risk. For example, in a longitudinal study of over 3,000 middle aged to older U.S. adults, Santini et al. (2020) found that social isolation and social disconnectedness were strongly associated with anxiety and depressive symptoms (Santini et al., 2020). Another 10-year retrospective study of U.S. adults (aged 25-75) found that risk of depression was significantly greater among those who reported high social strain at baseline, lack of social support at baseline, and poor overall relationship quality at baseline data collection. In this study, individuals who reported the lowest overall quality of social relationships had greater than double the risk of depression at the end of the study, compared to those who reported the highest quality of social relationships (Teo et al., 2013).

Studies conducted during the COVID-19 pandemic have also shown that social isolation may be associated with increased anxiety and depression. For example, a recent survey-based study conducted by Robb et al. in the United Kingdom found a significant negative association between subjective loneliness and higher depression and anxiety symptoms during the COVID-19 outbreak (Robb et al., 2020). In a recent survey-based study of over 20,000 individuals from Asia, Europe, and the U.S., researchers found that individuals, and in particular older individuals, reported higher levels of physical or mental health ailments, such as depression or anxiety, due to social isolation and social distancing during COVID-19 (Sepulveda-Loyola, 2020).

How social isolation leads to increased depression risk is not fully understood, however, research conducted in animal models lends insight into biological mechanisms which might explain the link between social isolation and depression risk. For example, prairie voles are

socially monogamous rodents that live in social colonies, and it has been suggested that prairie voles might therefore provide a valid animal model for understanding the biology of human social interaction (Grippe et al., 2007). Studies have suggested that, when socially isolated, prairie voles exhibit depressed appetite, depressive-like behaviors, and impaired neurogenesis (Grippe et al., 2007; Lieverwirth et al., 2012), similar behavioral and biological characteristics to what has been found in humans with MDD.

Moreover, experimental studies in humans suggest that social isolation leads to long-term adverse effects on brain structure and function, and neuroendocrine abnormalities. For example, fMRI studies show that, compared to individuals who report not being lonely, socially isolated or lonely individuals show decreased activation in the dorsomedial prefrontal cortex (responsible for inferring mental states) in response to viewing negative social scenes (Cacioppo, 2014). Other research has shown that when viewing pleasant stimuli, lonely individuals show less interest in social stimuli (as evidenced by decreased activation of the ventral striatum to pictures of people than of objects), whereas non-lonely individuals show stronger activation of the ventral striatum to pictures of people than of objects (Cacioppo, 2010). Moreover, MRI scans of socially isolated or lonely individuals have shown that individuals with higher loneliness scores on standardized questionnaires display smaller gray matter volumes in the amygdala, hippocampus, and cerebellum (Duzel et al., 2019).

It has been found that in both animals and humans, social isolation can result in increased activity of the HPA axis (Cacioppo, 2014). Social isolation has also been found to activate neural, neuroendocrine, and behavioral responses that encourage short-term self-preservation (Cacioppo, 2014). However, overactive or prolonged exposure to neuroendocrine-mediated

processes (such as cortisol release) has been shown to increase anxiety, hostility, social withdrawal, poor sleeping patterns, and decreased impulse control (Cacioppo, 2014).

Considering the profound increase in social isolation in individuals during the COVID-19 pandemic, strategies to reduce the impact of social isolation seem paramount, particularly with regards to reducing risk for depression. During COVID-19, there are several things that can be done to help combat social isolation and depression. It has been suggested that diet and physical activity may play key roles in combatting depression during social isolation (Sepulveda-Loyola et al., 2020).

Stress Buffering Effects of Physical Activity

Considering the major role of chronic stress in depression risk, interventions that positively impact behavioral and physiological stress regulation may also help to prevent the development of depression. Studies suggest that regular physical activity and/or exercise may positively affect both behavioral and physiological responses to stress (Crowley et al., 2020; Crowley et al., 2015; Klaperski et al., 2014; Jayasinghe et al., 2017). The hypothesis that the physiological response to regular exercise may help to regulate the physiological response to psychosocial stressors has been termed the “cross-stressor adaptation hypothesis” (Sothmann et al, 2006).

The major premise of the cross-stressor adaptation hypothesis suggests that repeated physiological responses to accumulated exercise bouts (exercise training) allows the body to better adapt, to similarly taxing states (such as mental stressors) (Sothmann et al., 2006). Several recent studies show support for the cross-stressor adaptation hypothesis. For example, a recent study by Crowley et al (2020), found that higher cardiorespiratory fitness in women associated with a lower heart rate response to a laboratory-based psychosocial stressor, and improved sleep

quality (Crowley et al., 2020). In addition, a recent study by Klaperski et al. (2014) found that individuals who reported higher levels of moderate and vigorous intensity exercise exhibited lower heart rate and cortisol responses to a laboratory-based psychosocial stressor (Klaperski et al., 2014).

Studies also suggest that acute bouts of exercise elicit stress responses similar to that of mental stressors. For example, a recent study by Zschucke et al. (2015) showed that when young men were exposed to a mental stressor (the Montreal Imaging Stress Task) following a 30-minute moderate intensity exercise bout vs. a 30-minute placebo exercise, the men who were exposed to the 30 minute moderate intensity exercise bout exhibited a largely reduced cortisol response in response to the mental stressor battery (Zschucke et al., 2015).

Studies conducted using animal models have also suggested that physical activity/exercise may help to buffer the negative effects of psychosocial stress. For example, a study by Cox et al. (1991) showed that, when swimming, rats showed a reduced heart rate and plasma norepinephrine levels in response to foot shock stress (Cox, 1991), compared to non-exercising rats. Another study by Campeau et al. (2010), showed that six weeks of voluntary wheel running in rats reduced cortisol levels in response to mild stressors (such as, saline injections, and exposure to an experiment lab or moderate intensity noise) (Campeau et al., 2010).

Survey-based studies in humans have also shown that regular physical activity or exercise may reduce levels of perceived stress. For example, Aldana et al. (1996), studied the relationships between leisure time, physical activity, and perceived stress in 32,229 working adults. This study found that participants who burned an average of 3.0 Kcal per day by participating in leisure-time physical activity were between 0.78 and 0.62 times less likely to

report moderate to high perceived stress (Aldana et al., 1996). Further, a cross-sectional study in college populations also showed a positive impact of regular physical activity on perceived stress (Nguyen-Michel et al., 2006). In this study of 814 male and female college students, regular physical activity was associated with lower levels of perceived stress in response to daily hassles reported (Nguyen-Michel et al., 2006).

Not all studies have shown a positive effect of regular physical activity on levels of perceived stress. For example, a recent meta-analysis of randomized controlled trials that included exercise interventions and self-report measures of perceived stress in women (mean age 47.0 ± 1.7 years minimum to 71.8 ± 5.6 maximum) found no significant effect of physical activity on perceived stress in mid-life and older women (SMD: -0.16 ; 95% CI: -0.43 to 0.11). (Nigdelis et al., 2018). However, taken as a whole, the bulk of the evidence supports the hypothesis that regular exercise has a positive effect on physiological and behavioral responses to psychosocial stressors.

Barriers to Physical Activity during the COVID-19 Pandemic

One of the biggest challenges in physical activity promotion is getting individuals to initiate and/or maintain physical activity behavior. Behavior change is complex and is influenced by a multitude of factors including personal, social, environmental, and other factors. For PA behavior, in particular, the most commonly reported barriers to the initiation and/or maintenance of PA behavior include- time/scheduling barriers, financial barriers, social support barriers, environmental/community barriers, lack of knowledge about exercise, lack of motivation, and lack of resources/facilities for PA engagement (Salmon et al., 2003; Reichert et al., 2005; Arzu et al., 2006; Justine et al., 2013).

How the COVID-19 pandemic, and the associated NC stay at home order, has affected PA behavior is not yet understood, however, there have been some recent studies which have helped to shed light on the impact of COVID-19 on PA behavior. For example, in a recent study by Ng et al., the researchers sought to examine PA engagement and barriers to PA participation in school aged children during COVID-19-related school closures (Ng et al., 2020). In this cross-sectional study of 1,214 Irish students (aged 12-18 years), 50% of school-aged children in Ireland reported that they were less active than when in school, 30% reported no change in their PA levels, and 20% reported doing more PA during school closures (Ng et al., 2020). The researchers also found that the adolescents who were less active than they were in school were more likely to be overweight or obese compared to those that had no change in their PA levels or participated in more PA during school closures (Ng et al., 2020). In this study participants who were less active during school closures cited cancelled club training, and lack of time as major barriers to PA (Ng et al., 2020). This study suggests that for some vulnerable groups, lack of access to socially mediated exercise programs, can be detrimental to PA participation (Ng et al., 2020).

Atkinson et al. (2020), studied PA behavior in pregnant women during the COVID-19 pandemic. The American College of Obstetrics and Gynecology (ACOG) recommends that pregnant mothers should follow guidelines from the American College of Sports Medicine and the Department of Health and Human Services which recommend regular physical activity (at least 150 minutes of moderate intensity aerobic activity per week) during pregnancy and the postpartum period (Birsner et al., 2015). However, In the UK, in March 2020, pregnant women were deemed “at risk,” for severe illness from COVID-19 and it was recommended that they limit non-essential travel and activities. (Atkinson et al., 2020). Similar recommendations were

suggested by the CDC in the U.S. (Centers for Disease Control and Prevention, 2020). In the UK, Atkinson et al. found that pregnant women reported an increase in depressive and anxious symptoms during the COVID-19 pandemic, and also reduced levels of PA (Atkinson et al., 2020). In examining the association between PA and depressive and anxious symptoms in pregnant women in the UK, they found that women who exercised for at least 150 minutes per week reported a significantly smaller amount of depressive and anxious symptoms than the women who participated in at least 50% less PA (Atkinson et al., 2020). The authors suggest that increased levels of social isolation, interrupted daily routines, and limited opportunities for PA likely contributed to the increased prevalence of physical inactivity in women who were pregnant and/or postpartum (Atkinson et al., 2020).

Due to the new and unique challenges associated with the COVID-19 pandemic, more research is needed to better understand the unique barriers and facilitators of PA behavior during this unprecedented event. This seems especially important in light of public health recommendations on the importance of staying physically active during the COVID-19 pandemic for mental health (Antunes et al., 2020), immunity protection (Yousfi et al., 2020), and overall health and well-being (Chen et al., 2020).

Physical Activity and the Prevention of Depression

The biological plausibility of regular exercise to serve as a stress buffer, and in so doing, help to prevent the development of depression is supported by epidemiological evidence which suggests that regular exercise may indeed help to prevent the development of depression (Pascoe et al., 2018). For example, a study by Sui et al. investigated the influence of cardiorespiratory fitness (CRF) on incidence of depressive symptoms in a large prospective cohort ($n > 14,000$) of men and women, who provided data for the Aerobic Center Longitudinal Study (ACLS), based

out of the Cooper Institute in Texas. The ACLS database contains more than 326,000 records from 116,000 individuals representing over 2,200,000 person-years of observation (Cooper, 2014). In this study, Sui et al. grouped individuals from the ACLS dataset by their performance on a graded maximal treadmill exercise test (performed between 1970 and 1990) as low, moderate, or highly fit. Survey data on depressive symptoms [assessed via the 20-item Center for Epidemiologic Studies Depression Scale (CES-D)], was obtained approximately 12 years later. In total there were 1,022 participants, which included 282 women out of 3,085 (9.1%) and 740 men out of 11,258 (6.5%) that were classified as exhibiting symptoms consistent with depression, according to the standardized cut point of ≥ 16 on the CES-D (Sui et al., 2009). In this cohort, depressive symptoms were 31% lower for men with moderate CRF, while the odds for developing depression were 51% lower for men with high CRF (Sui et al., 2009). In women, the odds of developing depression were 44% lower for women with moderate CRF and 54% lower for women with high CRF (Sui et al., 2009). This study suggests that higher CRF may be protective against the development of depression, even years later.

In a prospective cohort study by Dishman et al. (2012), examined the relationship between *decreased* CRF and depressive symptoms in in a cohort of 7,936 men and 1,261 women (ages 20-85). To do this, the investigators examined changes in participant CRF levels (obtained from graded maximal exercise tests recorded at four separate clinic visits between the years 1971 and 2006). At the end of the study, 446 cases of depression were reported in men, and 153 cases of depression were reported in women (Dishman et al., 2012). Interestingly, in men between the ages of 51 and 55, every one-minute decline in participants' endurance on the maximal exercise treadmill test was associated with an increase in the odds of developing depression by 2%. In women between the ages of 53 and 56, every one-minute decline in participants' endurance on

the maximal exercise treadmill test was associated with an increase in the odds of developing depression of 9.5%. This study suggests that maintaining CRF, especially during middle age, may be protective against the development of depression.

Other longitudinal studies show similar findings. For example, a recent study by Becofsky et al. (2015), suggests that low CRF is a better predictor of depressive symptoms than obesity or being overweight. In this study, the researchers found that, after controlling for initial fitness levels, body mass index (BMI), waist circumference, and body fat percentage (assessed via hydrostatic weighing, the sum of 7 skinfold measurements, or both measurements following standardized protocol), low fitness levels were significantly associated with increased risk for depressive symptoms, while measures of “fatness” were not (Becofsky et al., 2015). Some studies suggest that obesity is significantly associated with increased risk for depression, but this study suggests that this level of physical activity may be a better predictor of depression than obesity (Milaneschi et al., 2018; Nemiary et al., 2012; Roberts et al., 2000).

In a cohort study performed by Harvey et al. (2018), researchers investigated both the association between regular exercise and depression risk, and the dose-response relationship between exercise intensity and risk of depression. Healthy men and women, aged 20 years or older, who were depression-free at study baseline, were followed for eleven years (Harvey et al., 2018). In the first phase of this study, Harvey et al (2015), had participants complete a questionnaire to answer questions regarding lifestyle, and past medical experiences, as well as attend a physical examination where depressive symptoms were assessed. In this study, the researchers found that light to moderate leisure-time physical activity, such as swimming or walking, was associated with reduced risk of depression diagnosis (assessed via medical exam) 11 years later. Harvey et al concluded that even low levels of exercise may be protective against

the development of depression. In fact, they estimated that approximately 12% of future depression cases could be prevented by as little as one hour of light to moderate leisure-time PA per week (Harvey et al., 2018).

Other studies have also shown that CRF may be protective against the development of depression in chronically stressful environments. This may be particularly salient to the chronic stress environment of the COVID-19 pandemic. For example, Crowley et al found that soldiers ($n = 300$) who started U.S. Army basic combat training (BCT; a 9-week high stress environment) highly fit [according to the Army Physical Fitness Test (APFT)] had significantly reduced odds of developing depression during BCT (measured via the 20-item Center for Epidemiologic Studies Depression scale), compared to those categorized as low fit according to the APFT (Crowley et al., 2015). In fact, the odds of reporting depressive symptoms in soldiers in this study were 60% lower for soldiers who started BCT as highly fit, compared to those in the low fitness category (Crowley et al., 2015). The study authors concluded that being physically fit may be protective against the development of depression in high/chronic stress situations.

These findings are also supported by several meta-analytic reviews (Conn, V., 2010; Kandola et al., 2019; Schuch et al., 2018). Moreover, a recent systematic review of meta-analyses investigated the relationship between regular PA and depression risk by analyzing eight meta-analyses of 134 studies (representing approximately 2,015 participants) that investigated the relationship between regular PA and the development of depression. Six meta-analytic studies found a positive relationship between regular PA and depression risk (effect sizes ranging from -0.35 to -0.81), and two meta-analytic studies found little to no effect of regular PA on risk for depression (Hu et al., 2020). The authors concluded that regular PA has a moderate effect on risk of developing depressive symptoms (Hu et al., 2020).

In summary, these studies suggest that being physically fit, and/or regularly participating in PA may be protective against the development of depression. Some studies suggest that this association may remain, even after considering other factors that have typically been associated with risk of depression, including overweight/obesity and chronic stress. While the precise intensity of exercise needed to help protect against the development of depression is currently unknown, some studies suggest that even small amounts of light to moderate intensity exercise may help to reduce depression risk.

Study Methods

For the current study, recruitment efforts were targeted towards residents of North Carolina (NC) during the month of April, 2020, when the state of NC was under a state-wide stay at home order (Cooper, 2020). Potential participants were recruited via email listserv, word of mouth, and Facebook announcements. Participants were informed that if they completed this survey and a subsequent survey eight months later, they would be entered into a drawing to win a \$100.00 Amazon gift card. Interested participants accessed a Google documents survey using a link provided by the research team. The first page of the online survey included the consent form, where participants were required to type their name, indicating consent to participate in the study. The flow of participants through the study is depicted in figure 5, and also summarized below.



Figure 5. Flow of participants through the study.

In the seven days that the survey was open (April 21-April 27, 2020), two-hundred and twenty-five participants completed the online survey. Of these, 11 (4.8%) participants' data was removed on the basis of their zip code of residence being outside of the state of NC. Another 15 (6.6%) participants' data was removed from the study due to missing data for either the predictor variable (IPAQ data) or the main outcome variable (BDI-II). Upon evaluation of the survey data, six (2.6%) participants' IPAQ data were identified as extreme outliers (± 3 standard deviations from the mean). In total 193 (85.7%) participants were included in the analysis representing 29 counties in NC (see figure 6).

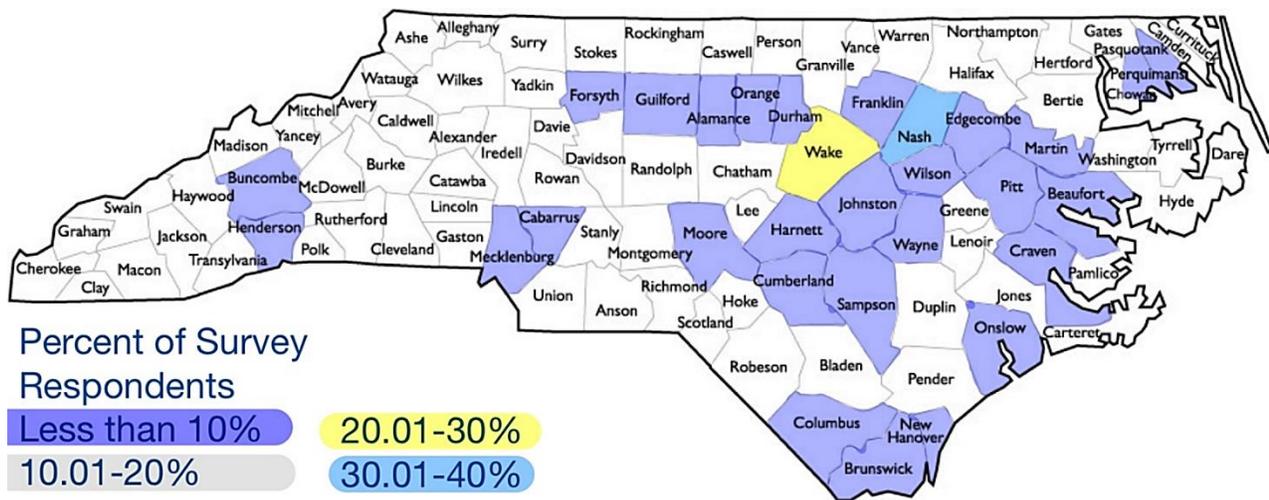


Figure 6. Distribution of survey responses across North Carolina.

The online survey included the following assessments: (1) depressive symptoms [assessed via the Beck Depression Inventory II (BDI-II; see Appendix B)]; (2) how often (never, rarely, sometimes, often, or very often) over the last month they accessed various PA resources including exercise programs on the internet, exercise programs on TV or video, exercise programs from printed sources, home fitness equipment, public health clubs or gyms, school or workplace gyms or fitness centers, and/or parks or open spaces; (3) PA activity over the last month (assessed via a 5 point likert scale ranging from “much lower” to “much higher” than usual); and (4) weekly PA participation [assessed via the International Physical Activity Questionnaire (IPAQ; see Appendix A)]. Participant inclusion criteria included being at least 18 years of age and possessing the ability to read and understand the participant consent form in English.

Standardized questionnaires used for assessments included the BDI-II and the IPAQ. The BDI is a 21 item (scale range 0-63) questionnaire that asks participants to indicate how they felt “during the past week, including today.” This is a well-validated scale that is commonly used to

assess depressive symptoms (Kuner et al., 2007) and typically takes about 5 minutes to complete. For this study, we used the short version of the IPAQ, which is a 7-item questionnaire, which elicits information on physical activity over the 'last seven-day' period (Hagströmer et al., 2006). The IPAQ has been used extensively to assess self-reported physical activity behaviors (Booth et al., 2003). Assessment of PA resources and categorical (e.g., higher than usual PA, lower than usual PA, etc.) PA activity over the last month were assessed using a question developed by the research team that was specific to this study. This question asked participants to rate their physical activity level over the last month according to a five response likert scale. Response options included the following: (1) much higher than usual; (2) higher than usual; (3) about the same as usual; (4) less than usual; (5) much less than usual. Participant responses were dichotomized into two groups: the same or higher than usual, and lower than usual. This measure was used to assess proportion of individuals reporting the same/higher or lower than usual PA during the COVID-19 pandemic, and to examine the association between self-reported PA activity category (the same/higher vs. lower) and duration of PA (assessed via the IPAQ).

Data reduction and analysis

For physical activity variables, total minutes/week of PA was calculated from the IPAQ, and PA activity likert scale results were dichotomized as (1) lower than usual or (2) the same/higher than usual. Descriptive statistics (means, standard deviations, and proportions) were conducted for demographic and behavioral characteristics of the study population. Independent t-tests were used to test for differences in minutes of PA (assessed via the IPAQ) between those who reported higher than usual PA and those who reported lower than usual PA, during the April, 2020 NC stay at home order. In order to investigate the relationship between PA and depressive symptoms, To test whether PA participation (total minutes PA/week, assessed via the

IPAQ) predicted depressive symptoms, multiple regression analysis was conducted using mean IPAQ score as the predictor variable, and mean BDI-II score as the outcome variable. We controlled for age, sex, body mass index (BMI), education, race, marital status, and income in the multiple regression model, as these variables have been shown in previous studies to be significantly associated with both PA level and depressive symptoms (Cooper et al., 2000; Dragan et al., 2007; Inaba et al., 2005; McArthur et al., 2009; Miech et al., 2000; Salk et al., 2017; Sallis et al., 1996; Sobal et al., 2010). All p-values reported were 2-sided with an alpha level of 0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Participant characteristics are shown in table 1. As illustrated in Table 1, the mean age for the participants was 35.6 ± 14.0 years of age. Approximately 25% of the participants were male, and approximately 75% of the participants were female. Mean BMI of the participants was $27.0 \pm 6.3 \text{ kg} \cdot \text{m}^{-2}$, the mean of which would be considered overweight (defined by BMI 25–29.9 $\text{kg} \cdot \text{m}^{-2}$). Mean BDI-II score for the participants was 9.3 ± 7.3 , and mean minutes of total PA/week was 443.7 ± 406.8 minutes.

Table 1 *Characteristics of study participants*

Participants, <i>n</i>	193
Age, years (mean \pm SD)	35.6 \pm 14
Sex	
Male, <i>n</i> (%)	48 (24.8)
Female, <i>n</i> (%)	145 (75.1)
Race	
African American, <i>n</i> (%)	25 (13.)
White, <i>n</i> (%)	161 (83.42)
Other, <i>n</i> (%)	7 (3.6)
Education	
< Bachelor's degree, <i>n</i> (%)	61 (31.6)
Bachelor's degree or higher, <i>n</i> (%)	132 (68.4)
Family income (annually)	
< \$50,000/year, <i>n</i> (%)	63 (32.6)
\geq \$50,000/year, <i>n</i> (%)	130 (67.4)
Employment	
Full time, <i>n</i> (%)	93 (48.2)
Part time, <i>n</i> (%)	20 (10.36)
Student, <i>n</i> (%)	59 (30.6)
Unemployed, <i>n</i> (%)	21 (10.9)
Marital Status	
Married, <i>n</i> (%)	96 (49.7)
Not married, <i>n</i> (%)	97 (50.3)
BMI (kg·m⁻²) (mean \pmSD)	27 \pm 6.3
BDI (mean \pmSD)	9.3 \pm 7.3
Total min/week PA (mean \pmSD)	443.7 \pm 406.8
Sitting [h/week (mean \pmSD)]	7.4 \pm 3.3
Walking [min/week (mean \pmSD)]	208.2 \pm 271.8
Moderate Intensity PA [min/week (mean \pmSD)]	112.1 \pm 141.4
Vigorous Intensity PA [min/week (mean \pmSD)]	123.4 \pm 126.2

BMI = body mass index, BDI = Beck Depression Inventory, min = minutes, PA = physical activity, h = hours

Of all participants included in the analyses, parks or open spaces and home fitness equipment were the most highly utilized PA resources in our participants during the April, 2020 NC stay at home order, followed by exercise programs on the internet (see figure 7).

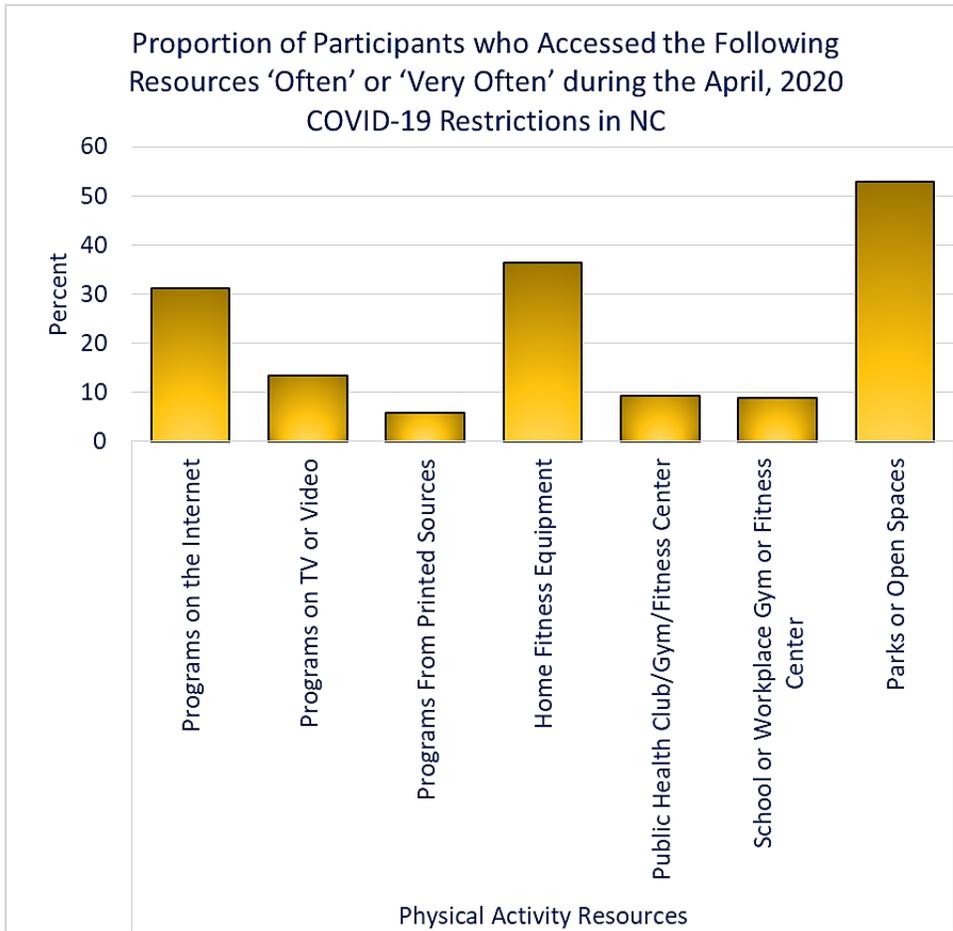


Figure 7. Distribution of physical activity resources used ‘often’ or ‘very often’ during the April, 2020 NC stay at home order.

Forty-four percent of participants reported that their PA levels were ‘lower than usual’ (reporting lower or much lower than usual) during the NC stay at home order (see figure 8).

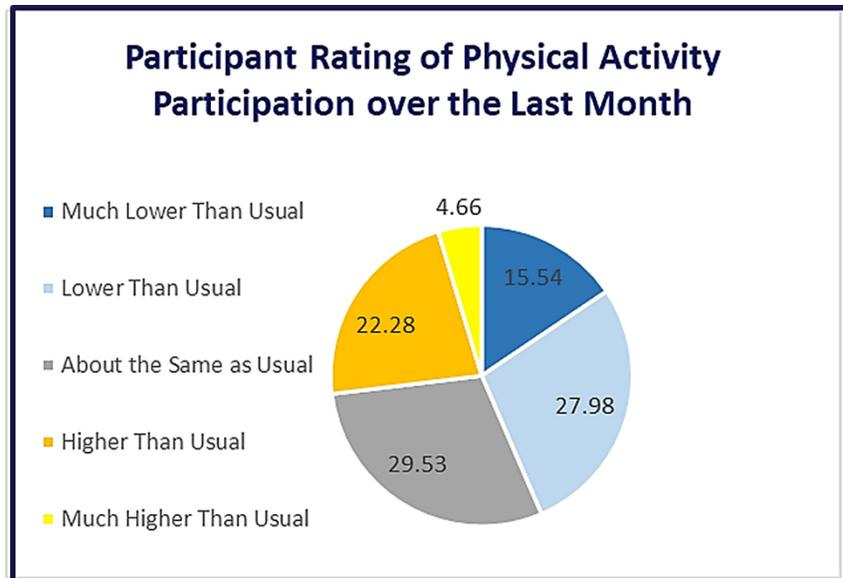


Figure 8: Change in PA levels during the April, 2020 COVID-10 stay at home orders in NC

Individuals who reported that their PA levels were lower than usual reported significantly lower durations of average PA over the last week, than those who reported that their PA levels were the same or higher (320.3 min/week vs. 538.7min/week; $t = -4.01$; $p < 0.001$; see figure 9).

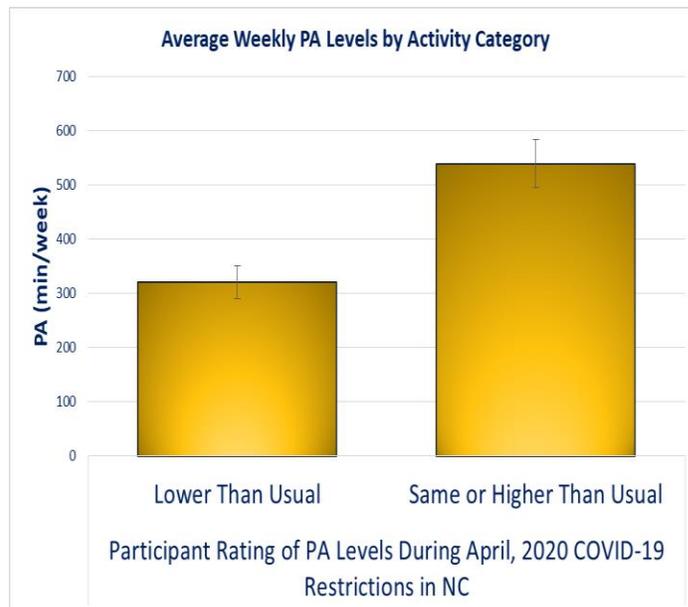


Figure 9: Average weekly PA duration by activity level. Values reflect mean +/- SEM; * $p < 0.0001$

Those who reported that their PA levels were lower than usual had significantly higher BDI scores (12.2 +/- 7.0 vs. 7.2 +/- 6.8, respectively) compared to those that reported that their PA levels were same or higher, during the April 2020 NC stay at home order ($t = 5.03$; $p < 0.0001$).

Regression analysis revealed that, after controlling for age, sex, BMI, education, race, marital status, and income, lower total PA duration per week significantly predicted higher depressive symptoms [$\beta = -0.19$, $p < 0.008$; see table 2 and figure 10 (simple linear regression graph)].

Predictor Variable	Model			
	Adjusted R ²	Standardized β	p-value for β	Model p-value
PA Duration (mean min/week)	0.18	-0.25	0.0006	< 0.001

Table 2. Multiple regression analysis for the prediction of depressive symptoms (BDI-II scores) by mean PA duration (minutes/week), adjusted for age, sex, body mass index, race, income, education, and marital status.

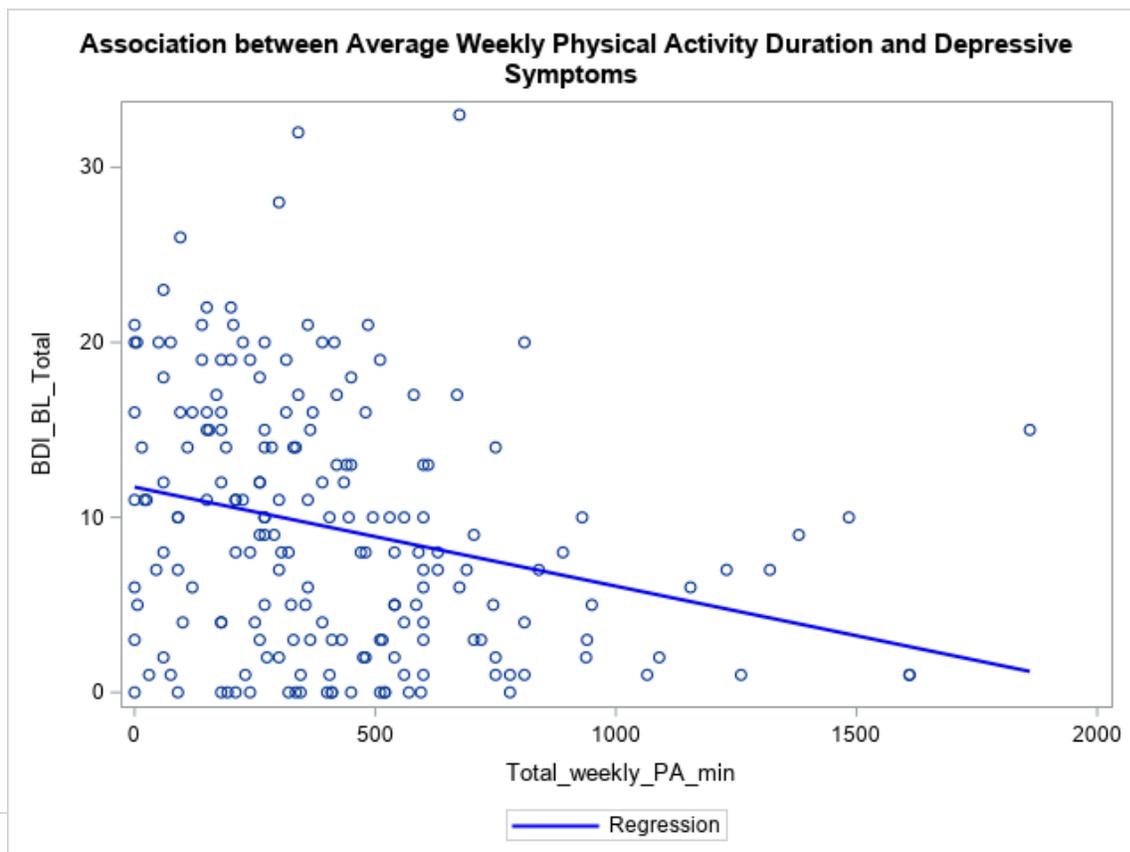


Figure 10: Simple regression model depicting the association between total weekly PA duration and depressive symptoms (measured via the BDI-II)

Discussion

A substantial proportion of individuals reported lower than usual PA during the NC stay at home order, which was associated with significantly reduced weekly PA durations. Consequently, lower weekly PA was associated with higher depressive symptoms in our study population. This finding remained significant, even after controlling for known covariates (age, sex, BMI, race, income, marital status). Our findings are in line with previous research that suggests that regular PA may be protective against the development of depression (Becofsky et al., 2015; Crowley et al., 2015; Dishman et al., 2012; Sui et al., 2009). Due to the cross-sectional nature of this study, it is not clear whether lower levels of PA led to increased depressive symptoms, or whether higher rates of depressive symptoms during COVID-19 negatively impacted PA behavior. For example, a recent study by Minaeva et al. (2020) found that objectively measured (via actigraphy) PA was significantly lower in individuals with diagnosed depression, compared to healthy age-matched controls. Another study by Sander et al., 2017, found that those that individuals who were both obese and depressed took less steps (about 6000 per day), compared to those that were obese and not depressed and those that were healthy (control group) (Sander et al., 2017).

Strengths of our study include the representation of participants across the state (including 29 counties in NC) and the use of well-validated standardized questionnaires. In addition, there were limitations to this study. Because this study was cross-sectional in nature, it

does not provide information about whether PA behavior was causal in the development of depressive symptoms during the COVID-19 pandemic. This cross sectional study simply provides a snapshot of participant responses at the time the survey was collected. Since temporal precedence is a strong criterion for determining causality, this study was not designed to provide evidence of causality, but rather information on the association between PA behavior and depressive symptoms during the COVID-19 pandemic. In addition, some studies suggest that PA self-report can be influenced by recall bias (Steen-Johannessen et al., 2016), perhaps reflecting social desirability by the participants. Social desirability is a type of response bias where survey respondents may answer questions in a manner that they think will be viewed favorably by the survey administrator (Crutzen et al. 2011). Thus, it is possible that the self-reported data in our study could be influenced by recall bias.

It is also possible that the high proportion of female respondents in our study (75.8% of survey respondents were female) could influence the results, considering that sex differences exist in both depression rates and PA participation between females and males (Hodes et al., 2016; Rosenfeld, 2016). In summary, these findings should be considered preliminary, considering the small sample size and use of self-report measures, but they suggest that future study of the unique barriers and facilitators of PA participation during the COVID-19 pandemic is warranted, particularly with regards to mental health outcomes.

Conclusion

Considering that 44% of survey respondents reported that their physical activity levels were lower than usual during the COVID-19 restrictions, and lower levels of physical activity were significantly associated with higher depressive symptoms, future study might consider

exploring the unique barriers to physical activity during the COVID-19 pandemic, and intervention strategies to help participants overcome these barriers, particularly with regards to mental health outcomes.

References

- Aldana, S.G., Sutton, L.D., Jacobson, B.H., Quirk, M.G. (February 1, 1996). Relationships between Leisure Time Physical Activity and Perceived Stress. *Perceptual and Motor Skills*. <https://journals.sagepub.com/doi/pdf/10.2466/pms.1996.82.1.315>
- Alen, N., Hostinar, C., (November 2018). Stress Effects on the Body. *American Psychological Association*. <https://www.apa.org/helpcenter/stress/effects-endocrine>
- Alschuler, L. (October 31, 2016). The HPA Axis. *Integrative Therapeutics*. <https://www.integrativepro.com/Resources/Integrative-Blog/2016/The-HPA-Axis>
- Antunes, R., & Frontini, R. (2021). Physical activity and mental health in Covid-19 times: an editorial. *Sleep medicine*, 77, 295–296. <https://doi.org/10.1016/j.sleep.2020.10.007>
- Arzu, D., Tuzun, E.H., Eker, L. (December 2006). Perceived Barriers to Physical Activity in University Students. *J Sports Sci Med*, 5(4), 615-620.
- Atkinson, L., De Vivo, M., Hayes, L., Hesketh, K.R., Mills, H., Newham, J.J., Olander, E.K., Smith, D.M. (October 2020). Encouraging Physical Activity during and after Pregnancy in the COVID-19 Era, and beyond. *International Journal of Environmental Research and Public Health*.
- Bancos, I. M.D. (December 2018). What is Serotonin? *Hormone Health Network*. <https://www.hormone.org/your-health-and-hormones/glands-and-hormones-a-to-z/hormones/serotonin>
- Becofsky, K.M., Sui, X., Lee, D-c., Wilcox, S., Zhang, J., Blair, S.N. (February 17, 2015). A Prospective Study of Fitness, Fatness, and Depressive Symptoms. *American Journal of Epidemiology*, 181(5), 311-320.
- Birsner, M.L., Gyamfi-Bannerman, C. (December 2015) Physical Activity and Exercise During

Pregnancy and the Postpartum Period. *Committee Opinion*, 804.

<https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/04/physical-activity-and-exercise-during-pregnancy-and-the-postpartum-period>

Boku, S., Nakagawa, S., Toda, H., & Hishimoto, A. (2018). Neural basis of major depressive disorder: beyond monoamine hypothesis. *Psychiatry and clinical neurosciences*, 72(1), 3-12. <https://pubmed.ncbi.nlm.nih.gov/28926161/>

Booth, M. L., Ainsworth, B. E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J. F., & Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Med sci sports Exerc*, 195(9131/03), 3508-1381.

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology*, 30(9), 846-856. <https://pubmed.ncbi.nlm.nih.gov/15961250/>

Cacioppo, J.T., Norris, C.J., Decety, G.M., Nusbaum, H. (May 17, 2010). In the Eye of the Beholder: Individual Differences in Perceived Social Isolation Predict Regional Brain Activation to Social Stimuli. *Journal of Cognitive Neuroscience*, 21(1).

<https://www.mitpressjournals.org/doi/abs/10.1162/jocn.2009.21007>

Cacioppo, J.T., Cacioppo, S., Capitanio, J.P., Cole, S.W. (August 22, 2014). The Neuroendocrinology of Social Isolation. *Annu Rev Psychol*, 66, 733-767.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5130104/>

Cacioppo, S., Capitanio, J.P., Cacioppo, J.T. (November 30, 2016). Toward a

- Neurology of Loneliness. *Psychol Bull*, 140(6), 1464-1504.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5130107/>
- Campeau, S., Nyhuis, T.J., Sasse, S.K., Kryskow, E.M., Herlihy, L., Masini, C.V., Babb, J.A., Greenwood, B.N., Fleshner, M., Day, H.E.W. (July 16, 2010). Hypothalamic Pituitary Adrenal Axis Responses to Low-Intensity Stressors are Reduced After Voluntary Wheel Running in Rats, *Journal of Neuroendocrinology*, 22(8).
- Centers for Disease Control and Prevention (December 2020). People with Certain Medical Conditions. *COVID-19*. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>
- Centers for Disease Control and Prevention (December 2020). Suggestions for Overcoming Physical Activity Barriers. *Physical Activity*.
<https://www.cdc.gov/physicalactivity/basics/adding-pa/barriers.html>
- Chen, P., Mao, L., Nassis, G. P., Harmer, P., Ainsworth, B. E., & Li, F. (2020). Coronavirus disease (COVID-19): The need to maintain regular physical activity while taking precautions. *Journal of sport and health science*, 9(2), 103–104.
<https://doi.org/10.1016/j.jshs.2020.02.001>
- Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol*. 2009 Jul;5(7):374-81. doi: 10.1038/nrendo.2009.106.
- Conn, V. (2010). Depressive symptom outcomes of physical activity interventions: Meta-analysis findings. *Annals of Behavioral Medicine*, 39(2), 128-138.
<http://dx.doi.org/10.1007/s12160-010-9172-x>
- Cooper, A., Page, A., Fox, K., & Misson, J. (2000). Physical activity patterns in normal,

- overweight and obese individuals using minute-by-minute accelerometry. *European Journal of Clinical Nutrition*, 54(12), 887-894. <https://doi.org/10.1038/sj.ejcn.1601116>
- Cooper, K. H. (2014). Cooper Center Longitudinal Study. *The Cooper Institute*.
- Cooper, R. (2020). State of North Carolina, Executive Order NO. 121.
<https://files.nc.gov/governor/documents/files/EO121-Stay-at-Home-Order-3.pdf>
- Cowen, P.J., Browning, M. (June 2015). What has serotonin to do with depression? *World Psychiatry*, 14(2), 158-160. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471964/>
- Cox, R.H. (1991). Exercise training and response to stress: insights from an animal model. *Medicine and Science in Sports and Exercise*, 23(7), 853-859.
https://journals.lww.com/acsm-msse/Abstract/1991/07000/Exercise_training_and_response_to_stress_insights.14.aspx
- Craft, L., Perna, F. (2004). The benefits of exercise for the clinically depressed. *Journal of Clinical Psychiatry*, 6(3), 104-111. [10.4088/pcc.v06n0301](https://doi.org/10.4088/pcc.v06n0301)
- Crowley SK, Girdler SS. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans? *Psychopharmacology (Berl)*. 2014 Sep;231(17):3619-34.
- Crowley, S., Wilkinson, L., Wigfall, L., Reynolds, A., Et Al. (2014). Physical Fitness and Depressive Symptoms during Army Basic Combat Training. National Institutes of Health. *NIH Public Access Author Manuscript*.
- Crowley, S.K., Wilkinson, L.L., Wigfall, L.T., Reynolds, A.M., Muraca, S.T., Glover, S.H.,

- Wooten, N.R., Sui, X., Beets, M.W., Durstine, J.L., Newman-Norlund, R.D., Youngstedt, S.D. (January 2015). Physical fitness and depressive symptoms during army combat training. *Med Sci Sports Exerc.*, 47(1), 151-158.
- Crowley, S. K., Rebellon, J., Huber, C., Leonard, A. J., Henderson, D., & Magal, M. (2020). Cardiorespiratory fitness, sleep, and physiological responses to stress in women. *European Journal of Sport Science*, 1-10.
- Crutzen, R., & Goritz, A. (2011). Does social desirability compromise self-reports of physical activity in web-based research? *International Journal of Behavioral Nutrition and Physical Activity*, 8(31). <https://doi.org/10.1186/1479-5868-8-31>
- Czeisler, M. É., Lane, R.I., MA, Petrosky, Emiko, MD, Et Al. (August 14, 2020). Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic – United States, June 24-30, 2020. *CDC Weekly*, 69(32);1049-1057.
<https://www.cdc.gov/mmwr/volumes/69/wr/mm6932a1.htm>
- Dahlitz, M. (January 4, 2017). Prefrontal Cortex. *The Science of Psychotherapy*.
<https://www.thescienceofpsychotherapy.com/prefrontal-cortex/>
- Dansinger, M. (July 1, 2019). What is Insulin Resistance?
<https://www.webmd.com/diabetes/insulin-resistance-syndrome>
- Delgado, P. L. (2000). Depression: The case for a monoamine deficiency. *The Journal of Clinical Psychiatry*, 61, 7-11. Retrieved from
<http://proxy.ncwc.edu/login?url=https://www-proquest-com.proxy.ncwc.edu/docview/208843582?accountid=12726>
- Department of Health (2004). Introduction to the monoamine system. *Models of intervention and*

care for psychostimulant users, 2(51).

<https://www1.health.gov.au/internet/publications/publishing.nsf/Content/drugtreat-pubs-modpsy-toc~drugtreat-pubs-modpsy-2~drugtreat-pubs-modpsy-2-3~drugtreat-pubs-modpsy-2-3-intr>

Dishman, R.K., Sui, X., Church, T.S., Hand, G.A., Trivedi, M.H., Blair, S.N. (October 2012).

Decline in Cardiorespiratory Fitness and Odds of Incident Depression. *American Journal of Preventive Medicine*, 43(4), 361-368.

Dragan, A., & Akhtar-Danesh, N. (2007). Relation between body mass index and depression: a structural equation modeling approach. *BMC Medical Research Methodology*, 7(1), 1-8.

Dunlavey, C.J. (June 15, 2018). Introduction to the Hypothalamix-Pituitary-Adrenal Axis:

Healthy and Dysregulated Stress Responses, Developmental Stress and

Neurodegeneration, *Journal of Undergraduate Neuroscience Education*, 16(2), 59-60.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6057754/#b5-june-16-r59>

Duzel, S., Drewelies, J., Gerstorf, D., Demuth, I., Steinhagen-Thiessen, E., Lindenberger, U.,

Kuhn, S. (September 19, 2019). Structural Brain Correlated of Loneliness among Older Adults. *Scientific Reports*, 9. <https://www.nature.com/articles/s41598-019-49888-2>

Flügge, G., van Kampen, M., & Mijster, M. J. (2004). Perturbations in brain monoamine

systems during stress. *Cell and tissue research*, 315(1), 1-14.

[https://books.google.com/books?id=RqtKykeXp6oC&pg=PT545&lpg=PT545&dq=Fl%C3%BCgge,+G.,+van+Kampen,+M.,+%26+Mijnster,+M.+J.+\(2004\).+Perturbations+in+brain+monoamine+systems+during+stress.+Cell+and+tissue+research,+315\(1\),+1-](https://books.google.com/books?id=RqtKykeXp6oC&pg=PT545&lpg=PT545&dq=Fl%C3%BCgge,+G.,+van+Kampen,+M.,+%26+Mijnster,+M.+J.+(2004).+Perturbations+in+brain+monoamine+systems+during+stress.+Cell+and+tissue+research,+315(1),+1-14.&source=bl&ots=8GXnQMNwd6&sig=ACfU3U3HVD-GShHVSBNk_MDnpI-X3H2YQ&hl=en&sa=X&ved=2ahUKEwIU5ZD0xv7sAhUOrVkKHUrNAvUQ6AEwAH)

[14.&source=bl&ots=8GXnQMNwd6&sig=ACfU3U3HVD-GShHVSBNk_MDnpI-](https://books.google.com/books?id=RqtKykeXp6oC&pg=PT545&lpg=PT545&dq=Fl%C3%BCgge,+G.,+van+Kampen,+M.,+%26+Mijnster,+M.+J.+(2004).+Perturbations+in+brain+monoamine+systems+during+stress.+Cell+and+tissue+research,+315(1),+1-14.&source=bl&ots=8GXnQMNwd6&sig=ACfU3U3HVD-GShHVSBNk_MDnpI-X3H2YQ&hl=en&sa=X&ved=2ahUKEwIU5ZD0xv7sAhUOrVkKHUrNAvUQ6AEwAH)

[X3H2YQ&hl=en&sa=X&ved=2ahUKEwIU5ZD0xv7sAhUOrVkKHUrNAvUQ6AEwAH](https://books.google.com/books?id=RqtKykeXp6oC&pg=PT545&lpg=PT545&dq=Fl%C3%BCgge,+G.,+van+Kampen,+M.,+%26+Mijnster,+M.+J.+(2004).+Perturbations+in+brain+monoamine+systems+during+stress.+Cell+and+tissue+research,+315(1),+1-14.&source=bl&ots=8GXnQMNwd6&sig=ACfU3U3HVD-GShHVSBNk_MDnpI-X3H2YQ&hl=en&sa=X&ved=2ahUKEwIU5ZD0xv7sAhUOrVkKHUrNAvUQ6AEwAH)

[X3H2YQ&hl=en&sa=X&ved=2ahUKEwIU5ZD0xv7sAhUOrVkKHUrNAvUQ6AEwAH](https://books.google.com/books?id=RqtKykeXp6oC&pg=PT545&lpg=PT545&dq=Fl%C3%BCgge,+G.,+van+Kampen,+M.,+%26+Mijnster,+M.+J.+(2004).+Perturbations+in+brain+monoamine+systems+during+stress.+Cell+and+tissue+research,+315(1),+1-14.&source=bl&ots=8GXnQMNwd6&sig=ACfU3U3HVD-GShHVSBNk_MDnpI-X3H2YQ&hl=en&sa=X&ved=2ahUKEwIU5ZD0xv7sAhUOrVkKHUrNAvUQ6AEwAH)

oECAIQAg#v=onepage&q=Fl%C3%BCgge%20G.%20van%20Kampen%20M.%20Mijnster%20M.%20J.%20(2004).%20Perturbations%20in%20brain%20monoamine%20systems%20during%20stress.%20Cell%20and%20tissue%20research%20315(1)%201-14.&f=false

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., ... & Reiser, M. (2006).

Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry and Neuroscience*, 31(5), 316.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1557684/>

Gaete, H.P., (October 5, 2016). Hypothalamus-pituitary-adrenal (HPA) axis, chronic stress, hair cortisol, metabolic syndrome and mindfulness. *Open Access Text*. DOI:

10.15761/IMM.1000244

Grippe, A.J., Cushing, B.S., Carter, C.S. (February 8, 2007). Depression-like behavior and stressor-induced neuroendocrine activation in female prairie voles exposed to chronic social isolation. *Psychosom Med*, 69(2), 149-157.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3006075/>

Hagströmer, M., Oja, P., & Sjöström, M. (2006). The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public health nutrition*, 9(6), 755–762. <https://doi.org/10.1079/phn2005898>

Harvey, S.B., Overland, S., Hatch, S.L., Wessely, S., Mykletun, A., Hotopf, M. (2018). Exercise and the Prevention of Depression: Results of the HUNT Cohort Study. *Am J Psychiatry*, 175, 28-36.

He, H., Sui, J., Du, Y. *et al.* (2017). Co-altered functional networks and brain structure in

- unmedicated patients with bipolar and major depressive disorders. *Brain Struct Funct* **222**, 4051–4064. <https://doi.org/10.1007/s00429-017-1451-x>
- Herbert, J. (May 8, 2012). Cortisol and depression: three questions for psychiatry. *Psychological Medicine*, *43*, 449-469.
https://www.researchgate.net/profile/Joe_Herbert/publication/224916674_Cortisol_and_depression_three_questions_for_psychiatry/links/569e230f08ae16fdf07c0f73/Cortisol-and-depression-three-questions-for-psychiatry.pdf
- Hirschfeld R. M. (2000). History and evolution of the monoamine hypothesis of depression. *The Journal of clinical psychiatry*, *61 Suppl 6*, 4–6.
- Hodes, G., Walker, D., Labonte, B., Nestler, E., Russo, S. (2016). Understanding the epigenetic basis of sex differences in depression. *Journal of Neuroscience Research*, *95*(1-2), 692-702. <https://doi.org/10.1002/jnr.23876>
- Huang, Y., Zhao, N. (2020). Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey, *Psychiatry Research*, Volume 288,112954,ISSN 0165-1781,
<https://doi.org/10.1016/j.psychres.2020.112954>.
- Inaba, A., Thoits, P. A., Ueno, K., Gove, W. R., Evenson, R. J., & Sloan, M. (2005). Depression in the United States and Japan: gender, marital status, and SES patterns. *Social science & medicine*, *61*(11), 2280-2292.
- Jackson, J.S., Knight, K.M., Rafferty, J.A. (September 20, 2009). Race and Unhealthy Behaviors: Chronic Stress, the HPA Axis, and Physical and Mental Health Disparities Over the Life Course. *American Public Health Association*.
<https://ajph.aphapublications.org/doi/full/10.2105/AJPH.2008.143446>

- Jayasinghe, S.U., Torres, S.J., Hussein, M., Fraser, S.F., Lambert, G.W., Turner, A.I (January 12, 2017). Fitter Women Did Not Have Attenuated Hemodynamic Responses to Psychological Stress Compared with Age-Matched Women with Lower Levels of Fitness. *PLoS ONE*, 12(1).
- Justine, M., Azizan, N.A., Hassan, V., Salleh, Z., Manaf, H. (October 2013). Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. *Singapore Med J*, 54(10), 581-586.
- Kandola, A., Ashdown-Franks, G., Stubbs, B., Osborn, D., & Hayes, J. F. (2019). The association between cardiorespiratory fitness and the incidence of common mental health disorders: A systematic review and meta-analysis. *Journal of affective disorders*, 257, 748–757. <https://doi.org/10.1016/j.jad.2019.07.088>
- Kang, L., Zhang, A., Sun, N., Liu, P., Yang, C., Li, G., Liu, Z., Wang, Y., Zhang, K. (October 19, 2018) *BMC Psychiatry*, 18(339).
<https://bmcp psychiatry.biomedcentral.com/articles/10.1186/s12888-018-1913-6>
- Kaufman, J., Plotsky, P.M., Nemeroff, C.B., Charney, D.S. (October 15, 2000). Effects of early adverse experiences on brain structure and function: clinical implications. *Biological Psychiatry*, 48(8), 778-790. [https://doi.org/10.1016/S0006-3223\(00\)00998-7](https://doi.org/10.1016/S0006-3223(00)00998-7)
- Klaperski, S., Dawans, B.V., Heinrichs, M., Fuchs, R., (2014). Effects of a 12-week endurance training program on the physiological response to psychosocial stress in men: a randomized controlled trial. *J Behav Med*, 37, 1118-1133.
- Kuner, C., Burger, C., Keller, F., & Hautzinger, M. (2007). Reliability and validity of the revised Beck Depression Inventory (BDI-II). Results from German samples. *Europe PMC*, 78(6), 651-656. [10.1007/s00115-006-2098-7](https://doi.org/10.1007/s00115-006-2098-7)

- Lange, C., & Irle, E. (2004). Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. *Psychological medicine*, 34(6), 1059.
<https://pubmed.ncbi.nlm.nih.gov/15554576/>
- Lee, D. Y., Kim, E., & Choi, M. H. (2015). Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. *BMB reports*, 48(4), 209–216.
<https://doi.org/10.5483/bmbrep.2015.48.4.275>
- Leuchter, A. F., Cook, I. A., Uijtdehaage, S. H., Dunkin, J., Lufkin, R. B., Anderson-Hanley, C., Abrams, M., Rosenberg-Thompson, S., O'Hara, R., Simon, S. L., Osato, S., & Babaie, A. (1997). Brain structure and function and the outcomes of treatment for depression. *The Journal of clinical psychiatry*, 58 Suppl 16, 22–31.
- Lieberwirth, C., Liu, Y., Jia, X., & Wang, Z. (2012). Social isolation impairs adult neurogenesis in the limbic system and alters behaviors in female prairie voles. *Hormones and behavior*, 62(4), 357-366. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565461/>
- [Ligouri, G., Feito, Y., Fountaine, C., & Roy, B. \(2021\). *Guidelines for Exercise Testing and Prescription*. Wolters Kluwer.](#)
- Marathe, S. V., D'almeida, P. L., Virmani, G., Bathini, P., & Alberi, L. (2018). Effects of Monoamines and Antidepressants on Astrocyte Physiology: Implications for Monoamine Hypothesis of Depression. *Journal of Experimental Neuroscience*. <https://doi.org/10.1177/1179069518789149>
- Martinsen, E.W. (2008). Physical activity in the prevention and treatment of anxiety and depression. *Nord J Psychiatry* 62. 25-29.
- Mayo Clinic Staff (March 19, 2019). Chronic Stress puts your health at risk.

<https://www.mayoclinic.org/healthy-lifestyle/stress-management/in-depth/stress/art-20046037>

Mayo Clinic Staff (July 24, 2019). Diabetes treatment: Using insulin to manage blood sugar.

<https://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/diabetes-treatment/art-20044084>

McArthur, L. H., & Raedeke, T. D. (2009). Race and sex differences in college student physical activity correlates. *American journal of health behavior*, 33(1), 80-90.

McEWEN, B.S. (1998). Stress, Adaptation, and Disease: Allostasis and Allostatic Load. *Annals of the New York Academy of Sciences*, 840: 33-44. doi:10.1111/j.1749-6632.1998.tb09546.x

McEwen, Bruce S. (August 01, 2003) Mood Disorders and allostatic load. *Mood Disorders and Medical Illness*, 54(3), 200-207. DOI:[https://doi.org/10.1016/S0006-3223\(03\)00177-X](https://doi.org/10.1016/S0006-3223(03)00177-X)

McEwen, B.S. (October, 2003). Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. *Metabolism*, 52(3), 10-16.

[https://doi.org/10.1016/S0026-0495\(03\)00295-6](https://doi.org/10.1016/S0026-0495(03)00295-6)

Miech, R. A., & Shanahan, M. J. (2000). Socioeconomic status and depression over the life course. *Journal of health and social behavior*, 162-176.

Milaneschi, Y., Simmons, K., van Rossum, E., & Penninx, B. (2018). Depression and obesity: Evidence of shared biological mechanisms. *Molecular Psychiatry*, 24, 18-33.

<https://doi.org/10.1038/s41380-018-0017-5>

Miller, C. M. (June 24, 2019). Onset of depression more complex than a brain chemical imbalance. *What causes depression?* Retrieved from <http://www.health.harvard.edu/newsweek/what-causes-depression.htm>.

- Miltmore, Jon. (2020). CDC: A Quarter of Young Adults Say They Contemplated Suicide This Summer During Pandemic. *Foundation for Economic Education*.
https://fee.org/articles/cdc-a-quarter-of-young-adults-say-they-contemplated-suicide-this-summer-during-pandemic/?fbclid=IwAR2pmAuurJltHHXXQkAC9adbnX7wZfXiLm35QPw8KIZJsRAIb4FTS_vEY28
- Minaeva, O., Booij, S., Lamers, F., Antypa, N., Schoevers, R., Wichers, M., & Riese, H. (2020). Level and timing of physical activity during normal daily life in depressed and non-depressed individuals. *Translational Psychiatry*, 10(259). <https://doi.org/10.1038/s41398-020-00952-w>
- Mittal, R., Debs, L.H., Patel, A.P., Nguyen, D., Patel, K., O'Connor, G., Grati, M., Mittal, J., Yan, D., Eshraghi, A.A., Deo, S.K., Daunert, S., Liu, X.Z. (April 10, 2017). Neurotransmitters: The critical modulators regulating gut-brain axis. *J Cell Physiology*, 232(9), 2359-2372. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5772764/>
- Murri, M., & Ekkekakis, P. (2020). Physical exercises: lowering mortality among patients with depression. *Psychiatric Times*. <https://www.psychiatristimes.com/view/physical-exercise-lowering-mortality-among-patients-depression>
- Nemiary, D., Shim, R., Mattox, G., & Holden, K. (2012). The relationship between obesity and depression among adolescents. *Psychiatric Annals*, 42(8), 305-308.
<https://doi.org/10.3928/00485713-20120806-09>
- Neumeister, A., Wood, S., Bonne, O., Nugent, A. C., Luckenbaugh, D. A., Young, T., ... &

Drevets, W. C. (2005). Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects. *Biological psychiatry*, 57(8), 935-937.

<https://pubmed.ncbi.nlm.nih.gov/15820716/>

[Newby, J., O'Moore, K., Tang, S., Christensen, H., & Faasse, K. \(2020\). Acute mental health responses during the COVID-19 pandemic in Australia. *PLoS One*, 15\(7\).](#)

DOI:10.1371/journal.pone.0236562

Ng, K., Cooper, J., McHale, F., Clifford, J., Woods, C. (April 2020). Barriers and facilitators to changes in adolescent physical activity during COVID-19. *BMJ Open Sport and Exercise Medicine*.

Nguyen-Michel, S.T., Unger, J.B., Hamilton, J., Spruijt-Metz, D. (August 16, 2006).

Associations between physical activity and perceived stress/hassles in college students.

Stress and Health, 22(3). <https://onlinelibrary.wiley.com/doi/abs/10.1002/smi.1094>

Nigdelis, M.P., Martinez-Dominguez, S.J., Goulis, D.G., Perez-Lopez, F.R. (August 2018).

Effect of programmed exercises on perceived stress in middle-aged and old women: a meta-analysis of randomized trials. *Maturitas*, 114, 1-8.

<https://www.sciencedirect.com/science/article/abs/pii/S0378512218302524>

Pan, K., Kok, A., Eikelenboom, M., Horsfall, M., Jorg, F., Luteijn, A., Rhebergen, D., van Oppen, P., Gitay, E., & Penninx, B. (2021). The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: A longitudinal study of three Dutch case-control cohorts. *The Lancet Psychiatry*, 8(2), 121-129. [https://doi.org/10.1016/S2215-0366\(20\)30491-0](https://doi.org/10.1016/S2215-0366(20)30491-0)

Pandya, M., Altinay, M., Malone Jr., D.A., Anand, Amit (December 14, 2012). Where in the

Brain is Depression? *Curr Psychiatry Rep.*, 14(6), 634-642.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3619732/>

Panchal, N., Kamal, R., Orgers, K., et al. (August 21, 2020) The Implications of COVID-19 for Mental Health and Substance Abuse. *Kaiser Family Foundation*.

<https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/>

Pascoe, M.C., Parker, A.G. (October 10, 2018). Physical activity and exercise as a universal depression prevention for young people: A narrative review. *Early Intervention in Psychiatry*, 13(4).

Phillips, J.R., Hewedi, D.H., Eissa, A.M., Moustafa, A.A., (May 5, 2015). The Cerebellum and Psychiatric Disorders. *Front Public Health*, 3, 66.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4419550/>

Pietrabissa, G., & Simpson, S. G. (2020). Psychological consequences of social isolation during COVID-19 outbreak. *Frontiers in Psychology*, 11, 2201.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7513674/>

Reichert, F.F., Barras, A.J.D., Domingues, M.R., Hallal, P.C. (October 2005). The Role of Perceived Barriers to Engagement in Leisure-Time Physical Activity. *AJPH American Public Health Association*.

Ressler, K.J. (June 15, 2010). Amygdala Activity, Fear, and Anxiety: Modulation by Stress. *Biological Psychiatry*, 67(12), 1117-1119.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882379/>

Robb, C. E., de Jager, C. A., Ahmadi-Abhari, S., Giannakopoulou, P., Udeh-Momoh, C.,

- McKeand, J., ... & Middleton, L. (2020). Associations of social isolation with anxiety and depression during the early COVID-19 pandemic: a survey of older adults in London, UK. *Frontiers in Psychiatry*, 11.
- Roberts, R., Kaplan, G., Shema, S., & Strawbridge, W. (2000). Are the obese at greater risk for depression? *American Journal of Epidemiology*, 152(2).
<https://doi.org/10.1093/aje/152.2.163>
- [Rosenfeld, C. \(2016\), Sex-dependent differences in voluntary physical activity. *Journal of Neuroscience Research*, 95\(1-2\), 279-290. <https://doi.org/10.1002/jnr.23896>](#)
- Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological bulletin*, 143(8), 783–822. <https://doi.org/10.1037/bul0000102>
- Sallis, J. F., Zakarian, J. M., Hovell, M. F., & Hofstetter, C. R. (1996). Ethnic, socioeconomic, and sex differences in physical activity among adolescents. *Journal of clinical epidemiology*, 49(2), 125-134.
- Salmon, J., Owen, N., Crawford, D., Bauman, A., & Sallis, J. F. (2003). Physical activity and sedentary behavior: A population-based study of barriers, enjoyment, and preference. *Health Psychology*, 22(2), 178–188. <https://doi.org/10.1037/0278-6133.22.2.178>
- Salters-Pedneault, K. (2020). The use of self-report data in psychology. *Very Well Mind*.
<https://www.verywellmind.com/definition-of-self-report-425267>
- Sanders, R. (February 11, 2014). New evidence that chronic stress predisposes brain to mental illness. Berkeley News, *Media relations*. <https://news.berkeley.edu/2014/02/11/chronic-stress-predisposes-brain-to-mental-illness/>

- Sanders, C., Ueck, P., Mergl, R., Gordon, G., Hegerl, U., Himmerich, H. (2017). Physical activity in depressed and non-depressed patients with obesity. *Eating and Weight Disorders- Studies on Anorexia, Bulimia and Obesity*, 23, 195-203.
<https://doi.org/10.1007/s40519-016-0347-8>
- Santini, Z.I., Jose, P.E., Cornwell, E.Y., Koyanagi, A., Nielson, L., Hinrichsen, C., Meilstrup, C., Madsen, K.R., Koushede, V. (January 3, 2020). Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis, *The Lancet: Public Health*, 5(1), 62-70.
<https://www.sciencedirect.com/science/article/pii/S2468266719302300#!>
- Schuch, F., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P., Silva, E., Hallgren, M., De Leon, A., Dunn, A., Deslandes, A., Fleck, M., Carvalho, A., & Stubbs, B. (2018). Physical activity and incident depression: A meta-analysis of prospective cohort studies. *The American Journal of Psychiatry*, 175(7), 631-648.
<https://doi.org/10.1176/appi.ajp.2018.17111194>
- Sepulveda-Loyola, W., Rodriguez-Sanchez, I., Perez-Rodrigues, P., Ganz, F., Torralba, R., Oliveira, D.V., Rodriguez-Manas, L. (September 25, 2020) Impact of Social Isolation Due to COVID-19 on Health in Older People: Mental and Physical Effects and Recommendations. *J Nutr Health Aging*, 1(10).
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7514226/>
- Singer, C. (2018). Health Effects of Social Isolation and Loneliness. *Journal of Aging Life Care*, 28(1).
https://www.aginglifecare.org/ALCA_Web_Docs/journal/ALCA%20Journal%20Spg18_FINAL.pdf#page=4

- Sobal, J., & Hanson, K. (2010). Marital status and physical activity in US adults. *International Journal of Sociology of the Family*, 181-198.
- Song, R.E., Lee, Y-S., Baek, J-D., Miller, M. (November 22, 2011). Physical Activity Status in Adults with Depression in the National Health and Nutrition Examination Survey, 2005-2006. *Public Health Nursing*, 29(3).
- Sothmann, M.S. (2006). The Cross-Stressor Adaptation Hypothesis and Exercise Training. *Psychobiology of physical activity*, 149-160. <https://psycnet.apa.org/record/2006-02237-010>
- Steen-Johannessen, J., Anderssen, S., Ploeg, H., Hendriksen, I., Donnelly, A., Brage, S., & Ekelund, U. (2016). Are self-report measures able to define individuals as physically active or inactive? *Medicine and Science in Sports and Exercise*, 48(2), 235-244. [10.1249/MSS.0000000000000760](https://doi.org/10.1249/MSS.0000000000000760)
- Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic medicine*, 73(2), 114-126. <https://www.psychiatry.wisc.edu/courses/Nitschke/seminar/Stetler%20&%20Miller,%20Psychosom%20Med%2073,%202011.pdf>
- Sui, X., Laditka, J.N., Church, T.S., Hardin, J.W., Chase, N., Davis, K., Blair, S.N. (February 2009). Prospective study of cardiorespiratory fitness and depressive symptoms in women and men. *Journal of Psychiatric Research*, 43(5), 546-552.
- Sults-Kolehmainen, M.A., Sinha, R. (2014). The Effects of Stress on Physical Activity and Exercise. *Sports Medicine*, 44, 81-121. <https://link.springer.com/article/10.1007/s40279-013-0090-5>

- Tafet, G.E., Idoyaga-Vargas, V.P., Abulafia, D.P., Calandria, J.M., Roffman, S.S., Chiovetta, A., Shinitzky, M. (2001). Correlation between cortisol level and serotonin uptake in patients with chronic stress and depression. *Cognitive, Affective, and Behavioral Neuroscience*, 1(4), 388-393. <https://doi.org/10.3758/CABN.1.4.388>
- Thau, L., Gandhi, J., Sharma, S. (May 20, 2020). Physiology, Cortisol. *Statpearls [Internet]*. <https://www.ncbi.nlm.nih.gov/books/NBK538239/>
- Teo, A., Choi, H., & Valenstein, M. (2013). Social relationships and depression: Ten-year follow-up from a nationally representative study. *PLoS One*, 8(4). [10.1371/journal.pone.0062396](https://doi.org/10.1371/journal.pone.0062396)
- Tiwari, P., Ruhela, S. (2012). Social Isolation & Depression among Adolescent: A Comparative Perspective, 2nd International Conference on Social Science and Humanity IPEDR, 31. <http://www.ipedr.com/vol31/048-ICSSH%202012-S10087.pdf>
- Torrico, T.J., Munakomi, S., (July 31, 2020). Neuroanatomy, Thalamus. *Statpearls [Internet]*. <https://www.ncbi.nlm.nih.gov/books/NBK542184/>
- Vandergriendt, C. (July 16, 2020). What's the Difference Between Dopamine and Serotonin? *Healthline*. <https://www.healthline.com/health/dopamine-vs-serotonin>
- Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry*, 161(11), 1957-1966. <https://pubmed.ncbi.nlm.nih.gov/15514393/>
- Vilagut, G., Forero, C.G., Barbaglia, G., Alonso, J. (May 2016). Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. *Plos One*.
- Webb, L. (2020). Covid- 19 lockdown: a perfect storm for older people's mental health. *Journal*

of psychiatric and mental health nursing.

<https://onlinelibrary.wiley.com/doi/10.1111/jpm.12644>

Wheeler, R.J. (1988). Identification of stress buffers. *Behav Med.*, 14(2), 78-89.

<https://pubmed.ncbi.nlm.nih.gov/3382777/>

Whitworth, J.A., Williamson, P.M., Mangos, G., Kelly, J.J. (December 2005). Cardiovascular Consequences of Cortisol Excess. *Vasc Health Risk Manag.* 1(4), 291-299.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1993964/>

Win, S., Parakh, K., Eze-Nliam, C., Gottdiener, J., Kop, W., Ziegelstein, R. (2010). Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: The cardiovascular health study. *Heart*, 97(6), 500-505.

<https://heart.bmj.com/content/97/6/500.info>

Yokoyama, K., Yamada, T., Mitani, H., Yamada, S., Pu, S., Yamanashi, T., Matsumura, H., Nakagome, K., Kaneko, K. (April 30, 2015). Relationship between hypothalamic-pituitary-adrenal axis dysregulation and insulin resistance in elderly patients with depression. *Psychiatry Research*, 226(2-3), 494-498.

<https://doi.org/10.1016/j.psychres.2015.01.026>

Yousfi, N., Bragazzi, N. L., Briki, W., Zmijewski, P., & Chamari, K. (2020). The COVID-19 pandemic: how to maintain a healthy immune system during the lockdown - a multidisciplinary approach with special focus on athletes. *Biology of sport*, 37(3), 211–216. <https://doi.org/10.5114/biol sport.2020.95125>

Zoppi, L. (January 23, 2019). Norepinephrine and Mental Health. *News Medical Life Sciences*.

<https://www.news-medical.net/health/Norepinephrine-and-Mental-Health.aspx>

Zorn, J. V., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol

stress reactivity across psychiatric disorders: a systematic review and meta-analysis.

Psychoneuroendocrinology, 77, 25-36. <https://pubmed.ncbi.nlm.nih.gov/28012291/>

Zschucke, E., Renneberg, B., Dimeo, F., Wustenberg, T., Strohle, A., (January 2015). The stress-buffering effect of acute exercise: Evidence for HPA axis negative feedback.

Psychoneuroendocrinology, 51, 414-425.

<https://www.sciencedirect.com/science/article/abs/pii/S030645301400403X>

Appendix A

IPAQ

Surveys average weekly PA participation [assessed via the International Physical Activity Questionnaire (IPAQ)].

Appendix B

BDI-II

The BDI-II surveyed depressive symptoms [assessed via the Beck Depression Inventory II (BDI-II)]; (2) how often (never, rarely, sometimes, often, or very often) over the last month they accessed various PA resources including exercise programs on the internet, exercise programs on TV or video, exercise programs from printed sources, home fitness equipment, public health clubs or gyms, school or workplace gyms or fitness centers, and/or parks or open spaces