UNIVERSITY OF CALGARY

Adolescent Mental Health: Canadian Psychiatric Risk and Outcome Study (PROCAN)-

Exercise Intervention Pilot Study

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN MEDICAL SCIENCES

CALGARY, ALBERTA

JANUARY, 2019

Abstract

BACKGROUND: The Canadian Psychiatric Risk and Outcome Study (PROCAN), a longitudinal study of youth at risk of serious mental illness (SMI), aims to better understand the trajectory of SMI. This study was conducted as a pilot exercise intervention on a subsample of the PROCAN cohort.

OBJECTIVES: The primary objective was to examine the feasibility of an exercise intervention in youth at risk of SMI. The secondary objectives were to determine whether symptoms of mental illness and memory would improve, and hippocampal volume would increase, following participation in a moderate to high intensity aerobic exercise program.

METHODS: Forty-four male and female youth at risk of SMI were recruited through the PROCAN project. Participants completed clinical, cognitive, neuroimaging and fitness assessments prior to and following a sixteen-week moderate to high intensity aerobic exercise intervention. Sixty-minute exercise sessions were held three times per week. Forty-one participants completed the entire intervention and assessments, including twenty-six that completed the neuroimaging portion. Twenty-eight age and gender matched healthy controls were recruited as a baseline comparison for neuroimaging.

RESULTS: Exclusion, consented, and retention rates were; 22.7, 57.6 and 93.2% respectively. Significant ($p < .05$) improvements in aerobic fitness ($p < .0001$) were achieved over the course of the intervention. Likewise, reductions in anxiety ($p = .024$), depression ($p = .012$), and general prodromal symptoms ($p < .0001$) occurred, however distress did not diminish ($p = .131$). Right whole ($p < .001$) and right anterior ($p = .001$) hippocampal volumes significantly increased. Forward Span ($p = .552$), Backward Span ($p = 1.000$) and Letter Number Span ($p = .606$) did not significantly change.

CONCLUSION: Aerobic exercise is a feasible and sound intervention strategy for reducing symptoms and improving overall physical health, including brain health, in youth at risk for SMI. Further research is required to replicate these findings and to expand knowledge of the mechanisms, optimum dose and factors that influence the efficacy of exercise.

Preface

This thesis is original, unpublished, independent research carried out by Syl Corbett. The research was covered by Ethics Certificate number REB15-1776, issued by the University of Calgary Conjoint Health Ethics Board for the project “Adolescent Mental Health: Canadian Psychiatric Risk and Outcome Study (PROCAN)-Exercise Intervention” on September 8, 2015.

Acknowledgements

Sincere thanks to the many that had a hand in helping execute this project. First and foremost, my supervisors Dr. Jean Addington and Dr. Glenda MacQueen, whose enduring support and guidance were instrumental from the onset. I am tremendously grateful for the opportunity they provided, and immensely appreciative for the exposure to the academic distinction, professionalism and composure they exemplify. It was truly an honor to learn from them. My colleagues in Dr. Addington's lab deserve much credit for rallying to make this endeavor a success.

I thank my committee members, Dr. Mark Swain and Dr. Signe Bray, whose input served to shape the direction of the project and taught me the importance of impartiality and critical research analysis. Their valuable insights and scientific acumen helped me gain perspective, which will undoubtedly continue to better my work. My external examiner, Dr. Penny Werthner, Dean of Kinesiology at the University of Calgary, graciously committed her time. Dr. Werthner's questioning and commentary were greatly respected and welcomed.

Brain Canada and the Mathison Centre for Mental Health Research and Education provided the funding for this research thereby making the entire project possible. Their commitment to backing research such as this will undeniably advance the field of mental health. Allowing me to contribute through their support was a position highly coveted.

Finally, I am humbled by all the participants that challenged themselves and often overcame considerable adversity to take part in the project. They taught me what matters most.

Dedication

This work is dedicated to my family.

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List of Symbols, Abbreviations, & Nomenclature

Abbreviation	Definition
ACC	Anterior Cingulate Cortex
ADNI	Alzheimer's Disease Neuroimaging Initiative
APS	Attenuated Positive Symptoms
APSS	Attenuated Positive Symptom Syndrome
BDI-II	Beck’s Depression Inventory-II
BDNF	Brain-derived Neurotropic Factor
BET	Brain Extraction Tool
BIPS	Brief Intermittent Psychotic Syndrome
CA	Cornu Ammonis
CHR	Clinical High Risk
COPS	Criteria of Psychosis-Risk Syndromes
CPAFLA	Canadian Physical Activity, Fitness and Lifestyle Approach
CSEP	Canadian Society for Exercise Physiology
DLPFC	Dorsolateral Prefrontal Cortex
DSM-5	Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion Tensor Imaging
EADC	European Alzheimer's Disease Consortium
fMRI	Functional Magnetic Resonance Imaging
FAST	FMRIB’s Automated Segmentation Tool
FIRST	FMRIB’s Automated Sub-cortical Segmentation Tool
FLIRT	FMRIB’s Automated Linear Registration Tool
FNIRT	FMRIB’s Automated Non-linear Registration Tool
GRD	Genetic Risk and Deterioration Syndrome
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MDD	Major Depressive Disorder
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
PFC	Prefrontal Cortex
PROCAN	Canadian Psychiatric Risk and Outcome
QIDS	Quick Inventory of Depressive Symptomatology
RPE	Rate of Perceived Exertion
SSRI	Selective Serotonin Reuptake Inhibitor
SMI	Serious Mental Illness
SOPS	Scale of Psychosis-Risk Symptoms
VO2max	Maximal Oxygen Consumption
VPFC	Ventral Prefrontal Cortex
WHO	World Health Organization
WMS-III	Wechsler Memory Scale-Third Edition

1 INTRODUCTION

1.1 Background

1.1.1 Physical Benefits of Aerobic Exercise in Healthy Populations

Regular aerobic exercise has physiological benefits, regardless of gender, age, weight, or athletic prowess of those who engage in the exercise. Aerobic conditioning also forms the foundation necessary for countless sports activities. Physical effects of habitual aerobic exercise include: maintenance of a healthy body weight (Centers for Disease Control and Prevention, 2015), maintenance or normalization of a healthy blood pressure (American Heart Association, 2014) and glucose level (American Diabetes Association, 2013), a strengthened cardiorespiratory system (Swift et al., 2013), preserved bone density (Tobias et al., 2014) and an overall increase in physical functionality and capacity. As such, aerobic exercise is frequently identified as an intervention to reduce the risk or severity of somatic disorders that plague many populations including obesity, metabolic syndrome, type II diabetes, heart disease, hypertension and select types of cancers.

Animal studies suggest that aerobic exercise also promotes neurobiological changes such as increased resistance to brain insult (Stummer, et al., 1994), vascularization (Black, et al., 1990), neurotransmitters (Mora, et al., 2007), neurogenesis (van Praag et al., 2002), and angiogenesis (Black et al., 1990). Human studies have reported increased whole brain volume (Colcombe et al., 2006) and increased brain perfusion with exercise (Maas et al., 2015). There are a number of potential mechanisms through which exercise might improve brain function. As an example, increased perfusion can enhance local oxygen supplies and nutrients to neurons and equally, increased neuronal activity could increase perfusion (Maas et al., 2015).

1.1.2 Psychological Benefits of Aerobic Exercise in Healthy Populations

Regular aerobic exercise may enhance psychological well-being; numerous studies report improved psychological outcomes in healthy populations after partaking in regular aerobic exercise regimes. Reported psychological benefits include improved autonomy and purpose (Delextrat et al., 2015), improved cognition (Hogan et al., 2013; Rasmussen & Laumann, 2013), decreased depressive symptoms (DiLorenzo, 1999; Hassmen et al., 2000; Khanzada et al., 2015; King et al., 1989), and lower levels of tension and anxiety (Khanzada et al., 2015; Moses et al., 1989).

Amongst these positive outcomes, cognitive enhancement is of particular interest. One's cognitive capacities are related to education and professional achievement (Deary, Strand, Smith & Frenandes, 2007), happiness (Pe, Koval & Kuppens, 2013), stress and socioeconomic status (Evans & Schamberg, 2009). Cognition typically includes early information processing, attention, learning various forms of memory, language and executive functions (Trivedi, 2006). Physical activity training may particularly improve executive control processes such as, working memory, multi-tasking, scheduling, planning and dealing with ambiguity (Guiney & Machado, 2013; Tomporowski et al., 2011; Hillman, Erickson & Kramer, 2008). Improvements in working memory undoubtedly have broad benefits in daily functioning, playing a critical role in multiple high-level cognitive demands such as inference, decision-making, mental calculations and awareness (Baddeley, 2012). Aerobic activity may increase the speed of cognitive processing (Brisswalter, Collardeau, & Rene, 2002; Fontana, Mazzardo, Mokgothu, Furtado, & Gallaher, 2009; Tomoporowski, 2003). Acute bouts of aerobic exercise can also enhance cognition by increasing the efficacy of the attentional system (Hogan, Kiefer, Kubesch, Collins, Kilmartin & Brosnan, 2013; Hogan, O'Hora, Kiefer, Kubesch, Kilmartin, Collins, & Dimitrova, 2015).

Further evidence supporting aerobic training and cognition has also been derived from school settings. Research examining the relations between physical activity and academic performance suggest an increase in the amount of time dedicated to physical health-based activities during school hours is not accompanied by a decline in academic performance (Hillman, et al., 2008); rather, aerobic fitness has a positive correlation to academic achievement (Castelli, et al., 2007). Achievement in standardized tests, specifically of mathematics and reading, is positively related to physical fitness scores, measured using a progressive aerobic cardiovascular endurance test in school-aged children (California Department of Education Standards and Assessment Division, 2001).

The benefits of aerobic exercise do not appear to be limited to the developing brain. Aerobic exercise has positive effects on cognition in the elderly and may slow the cognitive decline of aging (Buchman et al., 2012; Kramer, Erickson & Colcombe, 2006).

Engagement in aerobic sports has also been associated with better performance in spatial memory in several older age groups (Sanchez-Horcajo, et al., 2015).

While there have been studies investigating the potential for cognitive benefits of aerobic exercise in children, the elderly and general adult populations, there is a paucity of research on exercise-induced cognitive changes in older adolescents and young adults. Many studies use youth simply as a comparison with older adults, as a basis for age-related deficits in cognition with ageing (Hillman, Erickson & Kramer, 2008). This is an interesting age group to examine for several reasons, including the fact that key brain regions continue to develop into adulthood. Late adolescence/young adulthood is also a period of vulnerability for onset of a variety of brain illnesses, including psychotic and mood disorders.

1.1.3 Benefits of Aerobic Exercise in Mental Illness

There is a a dramatic decrease in life expectancy for individuals who have mental illness (Chesney, Goodwin, & Fazel, 2014; Lawrence, Kisely, & Pais, 2010; Newman & Bland, 1991; Nordentoft et al., 2013; Walker, McGee, & Druss, 2015). Genetics, early adverse experiences, exposure to pharmacotherapy, symptom-specific consequences, and lifestyle factors, including physical inactivity, may all contribute to the association between mental illness and somatic disease (McCreadie, 2003; Newcomer, 2005; Joukamaa et al., 2006; Fritz-Wieacker et al., 2007; De Hert et al., 2012). Additionally, there is growing evidence of psychological benefits of exercise in those with mental illness. Aerobic exercise enhances cognition (Greer et al., 2015), improves coping strategies and quality of life (Knapen et al., 2015), and decreases symptoms (Kerling et al., 2015) in people with depression, a leading cause of disability worldwide (WHO, 2008). Several systematic reviews and meta-analyses in the past decade have examined exercise and depression, reporting exercise as having a moderate effect on symptoms, and thus supporting its use as an adjunctive treatment option (Cooney et al., 2013; Kvam et al., 2016; Mead et al., 2009: Rimer et al., 2012).

Aerobic exercise also improves cognitive functioning (Kimhy et al., 2015), decreases depression (Dauwan et al., 2015; Scheewe et al., 2013), lowers stress and anxiety (Vancampfort et al., 2011), enhances short term memory, and moderates the severity of negative symptoms (Beebe, et al., 2005; Acil et al., 2008; Gorczynski & Faulkner, 2010) in people with schizophrenia. Additionally, general psychiatric symptoms improve with aerobic exercise (Dauwan et al., 2015; Scheewe et al., 2013 Vancampfort et al., 2012).

1.1.4 The Importance of Studying Youth at Risk of Serious Mental Illness

The Canadian Mental Health Association reports that 10-20% of Canadian youth are affected by mental illness, which is the single most disabling group of disorders worldwide (Canadian Mental Health Association, 2016). Youth considered at risk for serious mental illness (SMI) include those with self-reported experiences of anxiety, depressive and/or psychotic symptoms, such as: confusion about reality states, feeling a loss of personal control of thoughts or ideas, feelings of suspicion or paranoia, hearing or seeing things that do not exist, and/or having difficulty communicating clearly. At-risk youth not given a discrete diagnosis of mental illness are marginalized (McGorry et al., 2007; Rickwood, Deane & Wilson, 2007) and access to treatment may be difficult (Rickwood, Deane & Wilson, 2007). Lack of treatment for this at-risk population, may jeopardize potentially positive illness trajectories.

1.1.5 Benefits of Aerobic Exercise in Youth at Risk for Serious Mental Illness

While there is evidence of the benefits of aerobic exercise for those with mental illness, much less known about the effectiveness of exercise in those considered at risk for SMI in terms of overall health and risk reduction. The onset of mental illness typically occurs between early teens to mid-twenties (Kessler et al., 2005), and the prevalence of mental disorders is also highest in this age range (Australian Bureau of Statistics, 2008). Moreover, mental illness is the main cause of lost years due to poor health, disability and death in youth (Gore et al., 2011). Despite the potential for both psychological and systemic benefit in those at risk for SMI, as well as research encouraging its use (Hsiung, et al., 2015), inquiry into exercise as a means of intervention in youth with mental illness is uncommon (McClough, et al., 2012). In the limited studies that exist, symptom reduction seen with exercise and depression in adults is consistent with its effectiveness in youth (Strong et al., 2005).

Psychological distress, unpleasent experiences that involve both anxiety and depression, may also be an indicative symptom of risk for SMI. Viewed separately, individuals with anxiety and depression symptoms may not meet diagnostic thresholds, but taken together have significant functional impairment (Katon & Roy-Byrne, 1991). Such distress is known to progress into physical health issues and more severe mental disorders (Puustinen et al., 2011; Robinson et al., 2004). Similar to healthy populations and those with mental illness, youth at risk for SMI likely stand to gain from the potential antidepressive and anxiolytic effects of aerobic exercise.

Sedentary behavior in adolescence may itself constitute an additional risk factor for psychopathology (Carli et al., 2014). The risk for depression in adulthood is increased in youth with low physical activity (McKercher & Schmidt, 2014) and poor cardiovascular fitness (Aberg et al., 2012). Similarly, a study of current exercise practices in individuals at a clinical high risk of psychosis (as articulated by Yung & McGorry, 1996) suggests that the high risk group exercises at lower rates than healthy controls (Deighton & Addington, 2015). Parker et al. suggest that treatments, such as exercise, are required to target sub-threshold levels of mental illness in young people and consequently reduce the risk of persistence and recurrence of mental illness in this group (2011).

A prodromal period of early symptoms often precedes psychosis (Yung & McGorry, 1996), possibly offering an opportunity for early intervention. Likewise, deficits in certain domains of cognition may represent non-specific vulnerabilities for psychiatric illness such as bipolar disorder (McKinnon, Cusi, & MacQueen, 2013), forming another conceivable opportunity for timely intervention.

1.1.6 Cognition in Youth at Risk for Serious Mental Illness

A review of the literature, including 23 studies of individuals at risk for psychosis, demonstrated impairment in cognition relative to healthy controls, which appears to remain stable over time (Addington & Barbato, 2012). In a separate meta-analysis of 18 studies, those at high risk showed impairment in general intelligence, executive functioning, verbal and visual memory, attention and working memory (Fusar-Poli et al., 2012). Less is known about cognition for those at risk of other disorders. Several studies have shown various facets of working memory are altered in youth at risk. Female university students with childhood abuse, a known risk factor for depression and anxiety disorders, have demonstrated impairment in working memory for positive emotion (Cromheeke et al., 2014). In students transitioning to university with a genetic high risk for depression (carriers of the methionine allele of the brain derived neurotrophic factor), lower working memory capacity was related to increased depressive symptoms (LeMoult et al., 2015). Likewise, youth at increased familial risk of depression, show abnormalities in the neural circuitry supporting working memory (Mannie et al., 2010).

1.1.7 A Rationale for Focusing on the Hippocampus

Cognitive processes are multimodal and involve various encephalic regions. As an example, several brain areas are thought to be essential in working memory (Fuster, 2012), most critically, the frontal and medial temporal lobes (Kaminski et al., 2017). The hippocampus, a structure in the medial temporal lobe, is inextricably linked with cognition. It contains the neural circuitry that subserves memory and learning and recent evidence from animal and neuroimaging studies suggests the function of this brain structure extends beyond long-term recognition and underlies task performance in multiple cognitive domains (Olsen et al., 2012), including working memory (Axmacher et al., 2007, 2010; Fuentemilla et al., 2010; Poch et al., 2011; Ranganath & D'Esposito, 2001). The hippocampi have differentially been implicated in the acquisition of new memories with spatial (non-verbal) primarily on the right (Smith & Milner, 1981) and verbal on the left (Frisk & Milner, 1990; Papanicolaou et al., 2002). Positive associations between bilateral hippocampal volumes on both memory measures, with nonverbal being most strongly associated, have been found in a memory clinic population that included older adults with cognitive impairment (Bonner-Jackson, Mahmoud, Miller & Banks, 2015).

In-depth study of the hippocampus has traditionally examined anatomical and functional subfields, specifically the cornu ammonis (CA) areas 1-4, the dentate gyrus (DG), the subiculum and the presubiculum. Recent research demonstrates that segmenting the hippocampus along the long axis reveals anatomically distinct anterior and posterior segments associated with various functional specialties (Poppenk et al., 2013). Research also suggests anterior and posterior segmental differences may be more explanatory than global differences (Malykhin & Coupland, 2015). This dichotomus view, driven by animal studies, suggests while the ventral hippocampus is thought to be involved in affect processing, the dorsal hippocampus is related to cognitive functions (Moser & Moser, 1998), notably spatial memory (Bannerman et al., 2004; Fanselow & Dong, 2010). The effects of aerobic exercise on cognition, such as spatial working memory, may preferentially and differentially impact the anterior and posterior hippocampal segments. Examining this structure segmentally, therefore, as well as a whole, may be more revealing than strictly total volumetric analysis. Hippocampal asymmetry is also linked with cognitive function. Woolard and Heckers (2012) found a right greater than left asymmetry in the anterior hippocampus that correlated with general cognitive function, therefore right and left volumes should be examined individually.

Spatial working memory is the component of working memory that affords temporary retention and manipulation of information related to space, whereas verbal working memory relates to words and abstractions using language. Not only related to hippocampal structure (Colom et al., 2013), successful spatial working memory requires the joint participation of the hippocampus and the prefrontal cortex (PFC) demonstrated in both animal models (Bahner et al., 2015; Izaki, Takita & Akema, 2008; Spellman et al., 2015) and humans (Geva et. al., 2016). Anatomical studies on animals have shown direct connections from the ventral CA1 region of the hippocampus and subiculum to the medial prefrontal and orbitofrontal cortices (Jay & Winter, 1991), while numerous functional Magnetic Resonance Imaging (fMRI) studies in children (Nelson et al., 2000) and adults (van Asselen et al., 2006; Smith & Jonides, 1997) have reported spatial working memory is dependent upon the hippocampus and dorsolateral prefrontal cortex (DLPFC).

With respect to structural analysis of the hippocampus, current neuroimaging techniques include automated software programs that extract regions of interest, including quantifying subfield volumes. Subfield analyses mandate high-resolution images to reveal distinct subfields. Without adequate resolution, automated methods may not provide entirely reliable and valid methods for such distinction. Manual tracing offers a method of analyzing neuroimages both reliably and accurately with training.

1.1.8 The Hippocampus and Mental Illness

The integrity of the hippocampus has been examined in a variety of mental illnesses (Chan et al., 2016; Knochel et al., 2014). Smaller hippocampal volumes are commonly found in people with major depressive disorder (Arnone et al., 2012; Bremner et al., 2000; Du et al., 2012; McKinnon, Yucel, Nazarov, & MacQueen, 2009; Neumeister et al., 2005; Sheline et al., 1996; Videbech & Ravnkilde, 2004), schizophrenia (Adriano et al., 2012; Csernansky et al., 1998; Fortino et al., 2009; Heckers, 2001; Nelson et al., 1998), and bipolar disorder (Otten & Meeter, 2015). Within these disorders, normalization of hippocampal function, and perhaps structure in some instances, may be associated with improvements in behavior and cognition (Jun et al., 2012).

Both anterior and posterior hippocampal regions have been differentially associated in mental illness. Larger posterior hippocampal volumes are seen in patients with major depressive disorder (MDD) who remit in comparison to those who do not (MacQueen, 2009). In schizophrenia, some studies report abberations in the anterior and others in the posterior hippocampus (Bilder et al., 1995; Narr et al., 2001; Narr et al., 2002; Szeszko et al., 2002, 2003; Pegues et al., 2003).

Not solely intrinsic, hippocampal aberrations are evident extrinsically in mental illness. Abnormalities in fronto-limbic circuits including the; DLPFC, ventral prefrontal cortex (VPFC), anterior cingulate cortex (ACC), amygdala and hippocampus, are implicated in the pathophysiology of MDD (Anand et al., 2009; Gong & He, 2015; Jin et. al., 2011; Peng et. al., 2014; Ye et. al., 2015; Zhang et. al., 2011). Disrupted structural and functional connectivity is also seen in the prefrontal-hippocampal circuit in first-episode, medication-naïve adolescents with MDD (Geng et al., 2016). Likewise, hippocampal-prefrontal disruption is evident in those at risk of psychosis and at the onset of schizophrenia (Benetti et al., 2009).

1.1.9 Impact of Aerobic Exercise on the Hippocampus

In animal studies, hippocampal-dependent spatial memory is improved with aerobic exercise as demonstrated in various maze navigation tasks (Fordyce & Farrar, 1991; van Praag, 2008). Similar improvements are seen in spatial pattern separation (Creer et al., 2010), fear conditioning (Falls et al., 2010), and novel object recognition (O'Callaghan et al., 2007). Research in humans has revealed aerobic exercise upregulates the expression of several neutrophins, notably, brain-derived neurotrophic factor (BDNF), a neurotrophin thought to play a significant role in hippocampal neurogenesis, synaptic plasticity and learning (Cotman & Berchtold, 2002; Neeper, et al., 1995; Vaynman, et al., 2004). The dentate gyrus, the brain region where neurogenesis selectively occurs, is implicated in the formation of new memories and increased neurogenesis in this structure is associated with improved spatial memory (Jessberger et al., 2009; Luo et al., 2007). Animal models are unable to assess the effects on distinctly human cognitive capacities, such as verbal learning.

In adult humans, processing speed, working memory, and spatial memory, are all improved by exercise (Voss et al., 2013). Spatial working memory in particular is sensitive to fitness (Erickson et al., 2009) and exercise effects (Erickson et al., 2011). A meta-analysis reported that improvements in memory performance also occur following acute exercise (Lambourne & Tomporowski, 2010). Enhanced memory capacity might have a positive effect on multiple cognitive processes given the involvement of memory in numerous cognitive tasks (Kane et al., 2004) although this association remains speculative (Chooi & Thompson, 2012; Owen et al., 2010; Redick et al., 2013; Shipstead et al., 2012). Similar to animal studies, BDNF increases with exercise in humans and higher BDNF levels have been associated with larger hippocampal volumes (Erickson et al., 2010). An increase in volume is not only apparent in longitudinal study of long-term aerobic exercise training in both healthy older (Erickson et al., 2011) and young adults, but is also modulated by the aerobic exercise itself (Thomas et al., 2016).

Aerobic exercise in healthy subjects improves cognitive functioning (Colcombe & Kramer, 2003; Hillman et al., 2008) possibly as a consequence of neurogenesis in the hippocampal dentate gyrus (Pereira et al., 2007). Aerobic exercise largely has an effect on the anterior hippocampus including the dentate gyrus and cornu ammonis (CA1) subfields, but a minimal effect on the posterior hippocampus (Erickson et al., 2011). The CA1 subfield also plays a critical role in memory and isolated dysfunction leads to significant anterograde and retrograde amnesia (Bartsch et al., 2010; Döhring et al., 2017; Rempel-Clower et al., 1996).

Cross-sectional studies have documented a relation between hippocampal volume, cardiorespiratory fitness, and cognitive performance in children (Chaddock et al., 2010) and older adults (Erickson et al., 2009). Additionally, studies have shown that physical fitness levels among preadolescent children are associated with larger hippocampal volumes, which in turn correlate with greater relational memory performance (Chaddock et al., 2010). Likewise, adolescents with higher physical fitness have more grey matter volume in the hippocampus and score better on cognitive testing, including better visuospatial learning, in comparison to their lesser aerobically fit peers (Chaddock et al., 2010; Herting & Nagel, 2012).

1.1.10 Hippocampal Response to Aerobic Exercise in Mental Illness

Physical exercise is associated with larger hippocampal volumes in first-episode schizophrenia (McEwen et al., 2015) and similarly, exercise therapy increases hippocampal volume in schizophrenia patients (Pajonk et al., 2010). Further to this, an increase in hippocampal volume is positively associated with increased maximal oxygen uptake, BDNF, verbal and spatial memory (Erickson et al., 2011) in this disorder. However, whether the volumes of the hippocampal subfields in youth at risk for SMI differ from healthy comparison subjects is unknown.

In a recent systematic review that probed neurobiological effects of exercise on depression (Schuch et al., 2016), authors reported only one study investigated hippocampal volume. Results showed no increase in hippocampal volume, however this study had poor participation with an average of one 45 minute session per week for the three-month protocol (Krogh et al., 2014). This dose is likely too low to induce significant change in aerobic fitness and future research should implement a more rigorous intervention to adequately evaluate its effectiveness.

1.2 Rationale

Unique, and distinctly advantageous to any other approach, aerobic exercise improves physical health concurrently with potentially ameliorating mental health. In comparison to pharmacological interventions, aerobic exercise has few adverse effects and it may be more accessible than psychological therapies such as cognitive behavior therapy. The potential utility of aerobic exercise is such that it may offer an acceptable, accessible and cost-effective intervention for reducing distress and mitigating risk in youth at risk of SMI.

While there are numerous other factors besides the ones highlighted that influence brain structure and function, as well as overall well-being, converging evidence suggests that aerobic exercise may increase hippocampal volume, enhance cognition, and possibly improve symptoms of distress, anxiety and/or attenuated psychotic symptoms. Youth at risk for SMI may benefit from the cognitive, emotional and health benefits that aerobic exercise may provide.

Conducting a pilot study prior to an elaborate randomized controlled trial is both a logical and prudent step with distinct advantages. Recruitment may be analyzed to determine the most efficient methods and timing of these methods providing the background to develop optimal recruitment strategies. Eligibility may be assessed in its appropriateness, e.g., being too restrictive. The process of enrollment may be scrutinized to discover potential barriers or allurements.

Crucial to the study's success, adherence may be evaluated and modifications may potentially be made to facilitate attendance. In pharmacological studies of psychiatric conditions, nonadherence is said to be comparable to those of patients with other long-term conditions (Bulloch & Patten, 2010; Cramer, 1998), that being between 30 and 50% (WHO, 2003). Nonadherence in exercise research trials can be as high as 50% (Dishman, 1998). In meta-analyses involving exercise trials and mental illness, research has demonstrated the dropout rate to be 26.7% in schizophrenia (Vancampfort et al., 2016) and 18.1% in depression (Stubbs et al., 2016).

Requirements and capacities of both the personnel and facilities may be gauged based on the response of the participants. Delivery of the program in terms of safety and effectiveness may be monitored and revised if warranted. Other potentially valuable information that may not have initially been envisioned may surface while conducting the pilot study. Overall, such an initiative may mitigate risk, influence the structure and improve the probability of success of a future larger study.

2 AIMS & HYPOTHESES

2.1 Aims

2.1.1 Feasibility

i. To retain at least two thirds of all participants that commenced for the duration of the study.

ii. To have all participants complete at least 75 minutes of vigorous or 150 minutes of moderate aerobic exercise or a combination of the two per week over the duration of the study.

2.1.2 Clinical, Cognition & Neuroimaging

To determine whether the following changes in outcome measures will occur from baseline to follow-up in youth at risk for SMI after participating in a moderate to high intensity aerobic exercise program:

i. Reduction in distress, symptoms of depression, anxiety and/or attenuated psychotic symptoms associated with increased risk of SMI
ii. Improvement in working memory
iii. Increase in total hippocampal and anteriorly distinct segment volumes

2.2 Hypotheses

2.2.1 Feasibility

i. At least two thirds of all participants that commenced will complete the study.
ii. All participants will complete at least 75 minutes of vigorous or 150 minutes of moderate aerobic exercise or a combination of the two per week over the duration of the study.

2.2.2 Clinical, Cognition & Neuroimaging

i. Distress, symptoms of depression, anxiety and/or attenuated psychotic symptoms associated with increased risk of SMI are diminished after participating in a moderate to high intensity aerobic exercise program.
ii. Working memory will improve from baseline to follow-up in youth at risk for SMI after participating in a moderate to high intensity aerobic exercise program.

iii. Total hippocampal and anteriorly distinct segment volumes will increase from baseline to follow-up in youth at risk for SMI after participating in a moderate to high intensity aerobic exercise program.

3 METHODS

3.1 Participants

3.1.1 PROCAN Sample

3.1.1.1 Description of the PROCAN Sample

Participants included 240 male and female youth 12 to 25 years of age that were part of The Canadian Psychiatric Risk and Outcome Study (PROCAN) (Addington, Goldstein, Wang et al., 2018). PROCAN is a two-site (Calgary & Toronto, Canada) longitudinal study of youth at risk of SMI that aims to better understand why some young people develop SMI and others do not.

Participants in PROCAN include healthy controls (*n* = 40), those at familial high-risk (*n* = 40), and those with concerns about changes in mood or who notice changes in their thinking, behavior or experiences, such as: confusion about what is real or imaginary, feeling not in control of their thoughts or ideas, feeling suspicious or paranoid, having experiences that may not be real, and having trouble communicating clearly (*n* = 160).

Participants are classified on stages depending on the severity of their symptoms. Stage 0 are healthy controls, that is, they have no symptoms and no familial risk of mental illness.

Stage 1 participants are aysmptomatic, however they are considered to be at a risk for psychotic or severe mood disorders. Stage 1 participants are not seeking help, however they are recruited based on any of the following: may be a first-degree relative of a proband, have a family history of mental illness in relatives other than first degree, have had a low birth weight or preterm delivery, had a history of childhood physical or sexual abuse, and/or a presence of a major developmental disorder.

Stage 2 participants are typically help seeking with non-specific recent or mild symptoms of anxiety or depression and having only a minor impact on their social, educational or occupational function. They may include those with earlier childhood-onset symptoms that have reappeared or worsened in adolesence. They may also include those with earlier onset attentional or neurodevelopmental disorders that experience anxiety or depressive symptoms in adolescence.

Stage 3 participants have more specific symptoms of brief psychotic phenomena, brief hypomania, moderate depression, severe anxiety or presence of self-harm. There may be evidence of moderate neuropsychological change or at least a moderate impact on social, educational and or employment functioning.

Included in the Stage 3 participants are those identified as clinical high-risk (CHR) based on the Criteria of Prodromal Syndromes (COPS) (McGlashan et al., 2010). Criteria for CHR comprises of three catagories of psychosis-risk syndromes: Attenuated Positive

Symptom Syndrome (APSS), Brief Intermittent Psychotic Symptoms (BIPS), and Genetic Risk and Deterioration (GRD).

- A diagnosis of APSS requires the presence of at least one recent attenuated positive symptom (APS) of sufficient severity and frequency. Must have at some point rated level 3, 4 or 5 on at least one of the positive symptom items (unusual thought content, suspiciousness, grandiosity, perceptual disturbances, or disorganized communication) on the Scale of Psychosis-Risk Symptoms (SOPS) (McGlashan et al., 2010). Symptoms must have occurred at least once a week in the past month and must not have been due to another disorder.
- A diagnosis of BIPS requires a frank brief or intermittent psychotic intensity symptom (SOPS score =6) that must at some point have been present at least several minutes a day at a frequency of at least once a month and must not have been due to another disorder.
- A diagnosis of GRD requires a combined genetic risk for a schizophrenic spectrum disorder and history of functional deterioration. The genetic risk criterion can be seen in the patient who has a first-degree relative with any affective or nonaffective psychotic disorder and/or the patient has ever met criteria for DSM-5 Schizotypal Personality Disorder. Functional deterioration is a 30% or greater drop in the Global Assessment of Functioning-GAF (Hall, 1995) score within a year.

3.1.1.2 Recruitment of the PROCAN Sample

200 participants were recruited for the Calgary arm of PROCAN. Recruitment methods in Calgary included the distribution of descriptive print material to school counselors and health care centers that may be in contact with help-seeking youth. Further print advertising was placed in local papers. Additionally, presentations were held for youth groups and the general public.

3.1.2 Exercise Sample

3.1.2.1 Description of the Exercise Sample

Participants in the exercise study included 44 symptomatic individuals that had consented and were enrolled in the PROCAN project in Calgary. Symptomatic individuals were Stage 2 (n = 16) and Stage 3 (n = 25), including several CHR participants (n = 16).

3.1.2.2 Recruitment of the Exercise Sample

Several recruitment approaches were utilized to obtain the exercise study sample. PROCAN research personnel routinely invited new and current PROCAN participants to join the exercise program. S. Corbett followed up and met with any individuals that expressed a positive response. The aforementioned PROCAN presentations to schools and the general public included a brief description of the exercise study and interested parties were invited to contact the research coordinators for additional information. Posters were placed across the University of Calgary campus, local coffee shops and recreation centers. The same artwork was posted digitally on social media outlets

(Facebook & Twitter). Newspaper ads were placed in the local paper. Word-of-mouth between siblings and friends was used in the latter part of the study.

3.1.2.3 Estimate of Required Sample Size

It was expected that the data collected would be normally distributed across each study variable. With a threshold effect size set at 0.05 (minimum effect size that is considered significant), with a statistical power of 0.80 and a significance of 0.05, an estimated sample size of 32 people would be required (Binu, Mayya, & Dhar, 2014; Howell, 1982). The dropout rate was projected to be 15%, thus increasing the sample size to 38. The recruitment goal was rounded to 40 to account for any unforeseeable loss and to best achieve study targets. Recruiting continued until this goal was met. Interest continued past the study targets, hence, time permitting, additional individuals were allowed to join the program.

3.1.2.4 Healthy Controls for Neuroimaging

Twenty-eight age and gender matched healthy individuals were obtained strictly for a neuroimaging comparison. These individuals did not participate in the exercise intervention. Twenty-three of these individuals were from PROCAN and an additional five were from a related imaging study, CANBIND (Canadian Biomarker Integration Network for Depression Study). CANBIND is a multi-site study investigating biomarkers and the prediction of treatment outcome in patients with Major Depressive Disorder (MDD).

3.1.3 Inclusion Exclusion Criteria

3.1.3.1 Inclusion Criteria for PROCAN Study

All participants were male or female aged 12 to 25 years of age.

1. Healthy controls
2. Help-seeking subjects with symptoms; non-specific symptoms of anxiety or depression. Symptoms may include subjective or objective evidence of mild neuropsychological deficits. Evidence of only recent or mild impacts of illness on social, educational or occupational function.
    - For anxiety, mild to moderate levels of arousal without significant or persistent avoidant behaviors.
    - For depression, mild to moderate levels of depressive ideation without specific features indicative of a more disabling disorder.
    - May include those with earlier childhood-onset symptoms who have re-presented or worsened during the adolescent period.
    - May include those with earlier neurodevelopmental or attentional disorders who now present with anxiety or depressive symptoms in the adolescent years.
    - Typically adolescent or early adult populations assessed in primary care or educational settings or identified by screening within relevant populations.
3. Attenuated syndromes; subjects with specific symptoms of brief psychotic phenomena, brief hypomania, moderate depression, severe anxiety or presence of self-harm. There may be subjective or objective evidence of at least moderate

neuropsychological change or moderate to severe impact of illness on social, education or employment functioning.

i. Met COPS criteria, including long standing symptoms.

ii. Subthreshold manic symptoms. This is a period of abnormally and persistently elevated, expansive or irritable mood, as well as at least 2 of the following (3 in the case of irritable mood) present for at least 4 hours per day in at least 2 consecutive days in the past 6 months:

- Inflated self-esteem or grandiosity
- Decreased need for sleep
- Much more talkative than usual or pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Distractability
- Increased goal directed activity or psychomotor agitation

iii. Moderate Major Depressive Disorder (MDD). Current Major Depressive Episode of moderate severity (i.e. 11-15 on the Quick Inventory of Depressive Symptomatology-QIDS; Rush et al., 2003) or severe depression (≥ 16 on the QIDS) lasting ≥1 week, but < 6 weeks as diagnosed on the Structured Clinical Interview for DSM 5 (American Psychiatric Association, 2015).

iv. Anxiety syndromes. Characterized by more severe symptoms and development of specific avoidant behaviors.

v. Self-harm. Presence of regular, deliberate self-harm without overt suicidal intent may occur in this stage. This includes impulsive low lethality overdose occurring in the context of psychosocial stressor and in the absence of severe depression.

3.1.3.2 Exclusion Criteria for PROCAN Study

None of the participants:

Met any of the following;

- Impaired intellectual functioning (i.e. IQ <70, however those with an IQ in the range of 65-69 will be included if their Wide Range Acheivement Test [Psychological Assessment Resources, Inc., 2006] reading score is >75)
- Traumatic Brain Injury rated 7 or above on the Traumatic Brain Injury screening instrument (Abdel-Malik et al., 2003).
- Past or current central nervous system disorder
- Substance use that is rated as severe

Healthy Controls: Did not have any of the symptoms that are described above in section 3.1.3.1 for the two symptomatic groups, i.e. help-seeking with symptoms and attenuated syndromes.

Help-seeking with symptoms participants: Did not meet any of the criteria for attenuated syndromes.

Discrete Disorders:

Individuals have experienced clear episodes of psychosis, mania, or severe depression. Individuals have met threshold for the disorder with moderate-severe symptoms and persistence over time, typically associated with significant neuropsychological deficits. The illness is clearly having a major impact on social, educational or occupational functioning.

- For psychotic disorders: Individuals must have had a clear psychotic syndrome for > one week.
- For mania: Individuals must have clearly had symptoms of mania >4 days during a specific illness event; hypomanic symptoms or brief hypomanic syndromes alone were not considered a discrete disorder.
- For anxiety disorders: Individuals must also have at least a moderately severe and concurrent depressive disorder, typically associated with marked agitation, fixed irrational beliefs, overvalued ideas or attenuated psychotic symptoms, or substantial and persistent substance misuse.
- For depression: Individuals need to have features indicative of more severe disorders including psychomotor retardation, agitation, impaired cognitive functioning, severe circadian dysfunction, psychotic features, brief hypomanic periods, severe neurovegetative changes, pathological guilt or severe suicidality.
- For co-morbid or mixed syndromes: Individuals must have had significant symptoms (depressive, manic, or psychotic) within the context of a more severe syndrome that is persisting and having a major impact on function. The co-morbidity may include alcohol or substance misuse, abnormal eating behavior, or other relevant psychological disorders.

3.1.3.3 Inclusion Criteria Specific to Exercise Study

i. Individuals understood and were willing to sign the consent (or assent for minors)

ii. Individuals had to have the capacity to walk quickly for twelve minutes without assistance

iii. Individuals had to be willing to undergo the initial brain scan for the PROCAN study and a second scan at the end of the exercise intervention if they did not have a medical device or condition as a contraindication to such medical imaging

3.1.3.4 Exclusion Criteria Specific to Exercise Study

i. Individuals with a medical condition that precluded exercising at a moderately hard intensity

ii. Any individual that was currently participating in a rigorous exercise program at least once per week

iii. Healthy controls must not have met any of the criteria for help-seeking individuals or for attenuated syndromes

3.2 Assessments

All assessments occurred both at baseline and at follow-up for the study participants. Control subjects only did the baseline neuroimaging assessments. Normative data were used for all other variable comparisons. A summary of all the study assessments and measures is listed in **Table 1**.

3.2.1 Clinical Assessments

A thorough evaluation of the individual's current psychological state included tests for adverse symptoms in select domains. Anxiety was assessed using the Social Interaction Anxiety Scale (Rodebaugh et al., 2006). Distress was assessed using the K-10 Distress Scale (Kessler et al., 2002) and depression was assessed using the Beck Depression Inventory-II (BDI-II) (Beck & Steer, 1996). The SOPS, part of the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010), was used to assess attenuated psychotic symptoms such as: unusual thought content/delusional ideas, suspiciousness, grandiose ideas, perceptual abnormalities/hallucinations and disorganized communication.

3.2.2 Cognitive Assessments

Spatial working memory was assessed using the Wechsler Memory Scale-Third Edition (WMS-III): Spatial Span (The Psychological Corporation, 1997), a selected test in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (Nuechterlein & Green, 2006).

The spatial working memory assessment is a board with numbered cubes placed at the participant's midline within arm's reach. The participant was asked to touch the cubes in the same sequence as demonstrated by the administrator. The test included eight levels of two trials each. The levels included number sequences consisting of two numbers in level one and increasing one number every level up to nine numbers in level eight. For each trial one point was given for a correct response and no points were given for an incorrect response. The maximum score was 16. The test was stopped when the participant scored no points for both trials in the same level. Once the test was stopped either due to errors or to task completion, a subsequent test was administered that was identical to the first test. However, the participant was required to touch the same cubes as the administrator in the reverse order. The scoring for this test was identical to the initial test. Combined, a maximum score on these tests was 32 points. Both the maintenance and manipulation components of working memory are required in this task (Baddeley, 1986).

The Letter Number Span (Gold et al., 1997) is another subset of the WMS-III that was used. This is a verbal working memory test whereby the particpant had to mentally reorder a series of numbers and letters from and then repeat them to the administrator. The numbers were to be repeated from smallest to largest and the letters were to be in alphabetical order. There were 6 levels of 4 trials in increasing difficulty. 1 point was given for every correct answer for a maximum of 24 points.

3.2.3 Health Assessments

Overall health measures assessed included: body weight, body composition, blood pressure, as well as a self-report questionnaire covering dietary, sleep and fitness habits. This assessment was administered on the first day and last day of the intervention.

3.2.4 Fitness Assessments

A specific assessment for the exercise study involved a submaximal prediction of aerobic capacity (VO2max) following the Canadian Physical Activity, Fitness and

Lifestyle Approach (CPAFLA) protocol, as outlined and accepted as a standard by the Canadian Society for Exercise Physiology (CSEP). Specifically, the Cooper Assessment of Maximal Oxygen Uptake (Cooper, 1968) was administered. VO2max was estimated based on the maximum meters an individual ambulated (run or walk or a combination of the two) on the treadmill in 12 minutes. Similarly, this assessment was administered on the first day and last day of the intervention.

3.2.5 Neuroimaging Assessments

3.2.5.1 Total Intracranial Volume

The ENIGMA protocol (http://enigma.ini.usc.edu) was used to automatically estimate total intracranial volume (ICV) using FSL 5.0.5 (www.fmrib.ox.ac.uk/fsl). Individual high-resolution T1-weighted images were skull-stripped with the brain extraction tool (BET) (Smith, 2002). Tissue-type segmentation was executed with FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). The aforementioned protocol is an atlas-based approach; therefore images were then normalized to MNI152 (Montreal Neurological Institute, Montreal, Canada) standard space by an initial affine using FMRIB's Linear Registration Tool (FLIRT) (Jenkinson et al., 2002) and followed by a non-linear registration tool (FNIRT) (Anderson et al., 2010). To account for compression or expansion, the images were then modulated. The normalized modulated images were smoothed with an isotropic Gaussian kernel that had a sigma of 3 mm. ICV was computed by taking the inverse of the determinant of the affine matrix.

3.2.5.2 Hippocampal Segmentation

The same high-resolution T1 brain-extracted images were used to measure total hippocampal volumes. The EADC (European Alzheimer's Disease Consortium)-ADNI (Alzheimer's Disease Neuroimaging Initiative) Harmonized Protocol (HarP) was used for manual segmentation (Boccardi et al., 2015). This protocol provides a valid tool to examine hippocampal pathologies (Apostolova et al., 2015; Frisoni et al., 2015). MultiTracer2 (Woods, 2003) was the software used to trace all the images. Images were magnified five times in the coronal plane and three times in the sagittal plane. A stylus and interactive monitor (Wacom Cintiq 22HD, Kazo-shi, Saitama, Japan) were used to facilitate manual tracing. Tracings progressed rostral to caudal on the coronal slices while cross-referencing with the axial and sagittal views. The Frust Volume function in MultiTracer2 computed the volumes by summing each segmented area multiplied by the slice thickness.

An external rater with a qualification level according to the EADC-ADNI HarP, manually performed all tracings. To test intra rater reliability, a randomly chosen scan was repeatedly measured fifteen times. Chronbach’s alpha revealed a reliability of .91. To test inter rater reliability, twenty-five scans were randomly selected and re-traced by S. Corbett, who had also completed formal training on the harmonized protocol. Chronbach’s alpha for these scans resulted in a reliability of .96.

All scans were additionally assessed with automated protocols to verify total volumes (Thyreau, Sato, Fukuda & Taki, 2018) and visualize any potential discrepancies with the manual tracings (Yushkevich et al., 2006). An automated analysis using

FreeSurfer version 6.0.0 was also performed on the scans to identify any subfields that were particularly responsible for the volume changes (http://surfer.nmr.mgh.harvard.edu).

Further hippocampal segmentation occurred on the long axis with the uncal apex used as the discernable landmark for delineation of anterior and posterior segments. The uncal apex is considered a standard landmark used in hippocampal volumetry (Poppenk et al., 2013). Segmenting the hippocampus along the long axis using manual tracing provides a method of analysis that is clearly defined, replicable, and does not necessitate as high a field magnet strength as is required for definitive delineation. Total intracranial volumes were captured to identify relative hippocampal volumes changes.

3.3 Exercise Intervention

The exercise protocol was aerobic activity executed at 12-14 RPE (Rate of Perceived Exertion-Borg, 1982) as a warm up for 10 minutes, followed by 45 minutes ≥15 RPE as the target intervention intensity, and cooling down with an additional 5 minutes at 10-12 RPE. The intervention was three times per week for 16 weeks for a total of 48 hours of formal exercise time over the course of the program. Exercise intensity was periodically checked manually by the supervising researcher, as well by using the heart rate sensors on the various pieces of exercise equipment.

Aerobic activities included: skipping, calisthenics, running on a treadmill and on stairs, rowing on an ergometer, cycling on a stationary bike, and also using an elliptical machine. Exercise sessions changed throughout the course of the intervention in terms of order and activity.

3.4 Procedures

3.4.1 Clinical Assessments

All clinical assessments were completed as part of the parent PROCAN study and were conducted in private rooms at the Mathison Centre for Mental Health Research and Education at the University of Calgary. All clinical assessments were conducted by clinical raters who are trained on all clinical measures and are tested annually for reliability on all structured measures.

3.4.2 Cognitive Assessments

Cognitive assessments typically occurred on the same day or within a few days of the clinical assessments. These assessments occurred at baseline and at the end of the study and were administered by trained clinical raters at the Mathison Centre.

3.4.3 Health Assessments

A health questionnaire was administered at the Mathison Centre on the first and last day of the intervention. Upon completion of the questionnaire, subjects were guided to another private room to have their body weight, blood pressure, and body composition measured.

3.4.4 Fitness Assessments

Fitness was assessed on the first and last day of the intervention. These assessments were administered at Kinetix, a fitness facility in the Teaching Research and Wellness building, on the University of Calgary campus. The testing protocol was explained to the participants, including a demonstration of the emergency stop button on the calibrated treadmill to be used. Participants were asked to cover as much distance as possible in 12 minutes. The grade was set at 1%, however the participant set their desired pace to walk, jog or run or any combination throughout the 12 minute period. Including a cool down period, the fitness assessment was less than 25 minutes in duration.

3.4.5 Neuroimaging Assessments

Neuroimaging using a 3-Tesla General Electric Discovery MR-750 scanner (General Electric Healthcare, Buckinghamshire, UK) occurred at baseline and post intervention at the Seaman Family Centre located within the Foothills Medical Centre in Calgary, Alberta. The assessment post intervention was in addition to testing conducted in the parent PROCAN project. This additional timepoint was essential to identify potential effects, including those correllated to symptomatic changes observed, that may have potentially diminished if only measured a year after baseline as outlined in the parent study. High-resolution T-1 weighted images were acquired with a resolution of 1x1x1 mm with the following parameters: TR=6.4ms; TE=2.8ms; TI=450ms, pixel bandwidth=260, matrix dimension=240x240; and flip angle=15°.

3.4.6 Exercise Intervention

Exercise sessions were supervised by S. Corbett, and on occasion, with the help of a research assistant at Kinetix, a fitness facility on the campus of University of

Calgary. This supervision ensured safety, as well as appropriate protocol execution in terms of time and intensity. This supervision also provided participants with a chance to have any of their questions answered. The intention was that this interactive approach would improve study adherence.

3.4.7 Resources

The exercise facility used had the capacity to accommodate eight participants at any one time. Necessary pieces of equipment were readily available for use. Hallways and stairwells adjacent to the facility were utilized when there were more than eight participants.

3.5 Statistical Analysis

Demographic characteristics (age and gender) were collected at baseline. Study data were collected at baseline and post-treatment (data were only collected on controls at baseline). Such data included: clinical information (i.e. distress, depression, anxiety, and attenuated psychotic symptom scores), cognitive assessment ratings (i.e., working memory scores) and neuroimaging information (i.e. total, right, left, anterior and posterior hippocampal volumes).

Two-tailed independent t-tests were used to determine whether there were significant differences at baseline between the treatment group and healthy controls. Two-tailed dependent t-tests were used to determine if there were significant changes between baseline and post-treatment in all outcome measures. Effect sizes (i.e. Cohen's d) were calculated for all changes in the outcome variables. A Shapiro-Wilk test was used to assess normality (Shapiro & Wilk, 1965). Wilcoxon-Signed Rank and Mann-Whitney tests were used for paired and unpaired non-parametric data respectively. Pearson's Correlations were performed to assess associations between the study variables. Lastly, intra-rater and inter-rater reliability of hippocampal tracings between two raters were calculated using Chronbach's Alpha (Chronbach, 1951). All of the above statistical analyses were performed using IBM SPSS v24.0 software.

4 RESULTS

4.1 Feasibility

Participants were recruited for the exercise study over a 17-month span. Reasons for declining participation were as follows: already being too active (*n* = 11), already in another group (*n* = 18), living too far away (*n* = 6), not having time (*n* = 5), not having interest (*n* = 31) and losing interest (*n* = 13). Newspaper ad placement resulted in the most recruits over the shortest period of time. 9 people enrolled (22.0% of participants) during the month-long placement.

Of the 128 eligible PROCAN participants, 44 commenced and 41 completed the exercise study. A CONSORT diagram depicting the overall exercise study is displayed in **Figure 1**. Exclusion, consented and retention percentages were 22.7%, 57.6%, and 93.2% respectively. A summary of this data is presented in **Table 2**.

Exercise participants achieved a mean of; *M (SD)* = 98.3 (26.1) minutes of high intensity and a mean of; *M (SD)* = 32.8 (8.7) minutes per week of moderate intensity aerobic exercise over the course of 16 weeks. The mean number of participants per session was *M (SD)* = 5.4 (4.6) with a mode of 2 and a range of 1 to 19.

4.2 Clinical

A summary of the sample's descriptive characteristics is presented in **Table 3**.

A summary of clinical improvements is presented in **Table 4.** Distress, depression and anxiety scores at baseline and post intervention were normally distributed. Mean baseline [21.3 (SD = 7.4)] and post intervention [20.6 (SD = 8.5)] distress scores did not significantly change; $t(39) = -1.5$, $p = .131$ (See **Figure 2**). There was a significant reduction in mean anxiety scores between baseline [27.1 (SD = 17.0)] and post intervention [24.4 (SD = 17.3)]; $t(40) = -2.3$, $p = .024$ (See **Figure 3**). Similarly, there was a significant reduction in mean depression scores between baseline [12.7 (SD = 9.5)] and post intervention [10.6 (SD = 11.4)]; $t(39) = -2.6$, $p = .012$ (See **Figure 4**).

A summary of the sample's scores on the Scale of Prodromal Symptom is presented in **Table 5**. This data had an abnormal distribution at baseline and post intervention; therefore, nonparametric tests were used for the analyses. For the variables that showed significant change, i.e. negative and general symptoms, specific symptoms were further analyzed to determine to drivers of this change. The Wilcoxon Signed-ranks test was used to determine significance of change on all the SOPS measures. There was no significant reduction in positive ($z = -1.9$, $p = .061$) or disorganization ($z = -.8$, $p = .386$) symptoms following the exercise intervention. There was however a significant reduction in overall negative symptoms following the exercise intervention; $z = -2.4$, $p = .015$. Specific negative symptoms varied in their significance. There was a significant reduction in Social Anhedonia; $z = -2.2$, $p = .032$ and Ideational Richness; $z = -2.2$, $p = .027$. There was no significant reduction in Avolition; $z = -1.5$, $p = .134$, Expression of Emotion; $z = -.4$, $p = .680$, nor Occupational Functioning; $z = -.2$, $p = .805$. Additionally, there was a significant reduction in overall general symptoms following the exercise intervention; $z = -5.2$, $p < .0001$. Specifically, Sleep Disturbance; $z = -2.7$, $p = .008$, Dysphoric Mood; $z = -4.0$, $p < .0001$, and Impaired Tolerance to Normal Stress; $z = -3.5$, $p < .0001$, all significantly reduced post intervention. Motor Disturbances did not significantly change; $z = -.6$, $p = .949$.

4.3 Cognition

All scores on the cognitive measures were normally distributed. Pre and post-intervention scores are presented in **Table 6.** For non-verbal working memory, there was no significant reduction in forward span scores; $t(37) = -.6$, $p = .55$, $d = .10$ and no significant increase in backward span scores; $t(37) = .0$, $p = 1.00$, $d = .00$. For verbal working memory there was no significant improvement; $t(37) = -.6$, $p = .55$, $d = .10$.

4.4 Physical Health

A summary of physical health measures at baseline and post intervention is presented in **Table 7.** Data were normally distributed at baseline and post intervention on all measures. Mean systolic and diastolic blood pressure values were M (SD) = 114 (11), M (SD) = 76 (11) at baseline, and post intervention M (SD) = 111 (11), M (SD) = 73 (9) respectively. The reductions in systolic $t(35) = -1.6$, $p = .126$, $d = .34$, and diastolic,

$t(35) = -1.4$, $p = .168$, $d = .27$, blood pressure, were not significant. Mean body fat percentages were M (SD) = 24.2 (7.8) at baseline and M (SD) = 22.1 (7.7) post intervention. There was a significant reduction in body fat from baseline to post intervention; $t(39) = -4.3$, $p < .001$, $d = .27$ (See **Figure 5**).

Mean estimates of aerobic fitness were M (SD) = 20.01 (7.17) ml/kg*min-^{1} at baseline and M (SD) = 30.99 (9.25) ml/kg*min-^{1} post intervention. This constituted a significant increase in aerobic fitness; $t(39) = 7.9$, $p < .0001$, $d = 1.25$ (See **Figure 6**).

4.5 Neuroimaging

A summary of descriptive characteristics of the sample that completed imaging is presented in **Table 8**.

4.5.1 Intracranial Volumes

Intracranial volumes were normally distributed at baseline and post intervention. Mean intracranial volumes were; [2065425 (SD = 72703) mm^3] and [2089637 (SD = 59550) mm^3] at baseline and post intervention, respectively. There was no significant change in volume; $t(25) = 1.7$, $p = .10$. A summary of the paired neuroimaging results is presented in **Table 9**. There was no significant difference in means at baseline between the exercise participants [2065425 (SD = 72703) mm^3] and the healthy controls [2073593 (SD = 49216) mm^3]; $t(52) = -0.5$, $p = .628$, $d = .13$. Likewise, there was no significant difference in means between the healthy controls at baseline [2073593 (SD = 49216) mm^3] and the exercise participants post intervention

[2089637 (*SD* = 59550) mm^3]; $t(52) = -1.1$, $p = .284$, $d = .29$. A summary of the non-paired neuroimaging results at baseline and post intervention is presented in **Table 10**.

4.5.2 Hippocampal Volumes

Hippocampal volumes were normally distributed at baseline and post intervention. A summary of the sample's mean hippocampal volumes at baseline and post intervention is presented in **Table 9** and **Figure 7**. A summary of the mean hippocampal volumes of the exercise participants in comparison to healthy controls at baseline and post intervention is presented in **Table 10** and **Figure 7**.

4.5.2.1 Left Hippocampal Volumes

There was a significant difference in means at baseline between the exercise participants [2924 (*SD* = 333) mm^3] and the healthy controls [3220 (*SD* = 339) mm^3]; $t(52) = 2.3$, $p = .002$, $d = .88$. The mean volume for the left hippocampus was [2924 (*SD* = 333) mm^3] at baseline and [2928 (*SD* = 396) mm^3] post intervention. There was no significant increase in volume from baseline to post intervention; $t(25) = 0.1$, $p = .940$, $d = .01$. There remained a significant difference in means between the healthy controls at baseline [3220 (*SD* = 339) mm^3] and the exercise participants post intervention [2928 (*SD* = 396) mm^3]; $t(52) = -2.9$, $p = .005$, $d = .79$, suggesting the left hippocampal volumes of the exercise participants did not normalize over the course of the intervention.

4.5.2.2 Left Anterior Hippocampal Volumes

There was no significant difference in means at baseline between the exercise participants [1759 (*SD* = 289) mm^3] and the healthy controls [1895 (*SD* = 256) mm^3];

t(52) = -1.8, *p* = .072, *d* = .50. The mean volume for the left anterior hippocampus was [1759 (*SD* = 289) mm^3] at baseline and [1786 (*SD* = 315) mm^3] post intervention. There was no significant increase in volume from baseline to post intervention; *t*(25) = 1.2, *p* = .241, *d* = .09. Similarly, there was no significant difference in means between the healthy controls at baseline [1895 (*SD* = 256) mm^3] and the exercise participants post intervention [1786 (*SD* = 315) mm^3]; *t*(52) = -1.4, *p* = .165, *d* = .38.

4.5.2.3 Left Posterior Hippocampal Volumes

There was a significant difference in means at baseline between the exercise participants [1166 (*SD* = 181) mm^3] and the healthy controls [1325 (*SD* = 215) mm^3]; *t*(52) = -3.0, *p* = .005, *d* = .80. The mean volume for the left posterior hippocampus was [1166 (*SD* = 181) mm^3] at baseline and [1142 (*SD* = 209) mm^3] post intervention. There was no significant change in volume from baseline to post intervention; *t*(25) = -0.9, *p* = .364, *d* = .12. There was also a significant difference in means between the healthy controls at baseline [1325 (*SD* = 215) mm^3] and the exercise participants post intervention [1142 (*SD* = 209) mm^3]; *t*(53) = -3.2, *p* = .002, *d* = .86.

4.5.2.4 Right Hippocampal Volumes

There was a significant difference in means at baseline between the exercise participants [3028 (*SD* = 364) mm^3] and the healthy controls [3266 (*SD* = 337) mm^3]; *t*(52) = -2.5, *p* = .016, *d* = .68. The mean volume for the right hippocampus was [3028 (*SD* = 364) mm^3] at baseline and [3144 (*SD* = 362) mm^3] post intervention. There was a significant increase in volume from baseline to post intervention; *t*(25) = 4.1, *p* < .001, *d*

= .32.There was no significant difference in means between the healthy controls at baseline [3266 (*SD* = 337) mm^3] and the exercise participants post intervention [3144 (*SD* = 362) mm^3]; $t(52) = -1.3$, $p = .207$, $d = .35$.

4.5.2.5 Right Anterior Hippocampal Volumes

There was no significant difference in means at baseline between the exercise participants [1885 (*SD* = 286) mm^3] and the healthy controls [2058 (*SD* = 262) mm^3]; $t(52) = -0.3$, $p = .776$, $d = .63$. The mean volume for the right anterior hippocampus was [1885 (*SD* = 286) mm^3] at baseline and [1939 (*SD* = 285) mm^3] post intervention. There was a significant increase in volume from pre to post intervention; $t(25) = 3.7$, $p = .001$, $d = .19$. There was no significant difference in means between the healthy controls at baseline [2058 (*SD* = 262) mm^3] and the exercise participants post intervention [1939 (*SD* = 285) mm^3]; $t(52) = -0.2$, $p = .866$, $d = .43$.

4.5.2.6 Right Posterior Hippocampal Volumes

There was a significant difference in means at baseline between the exercise participants [1143 (*SD* = 149) mm^3] and the healthy controls [1208 (*SD* = 157) mm^3]; $t(53) = -0.2$, $p = .853$, $d = .42$. The mean volume for the right posterior hippocampus was [1143 (*SD* = 149) mm^3] at baseline and [1206 (*SD* = 169) mm^3] post intervention. There was a significant increase in volume from pre to post intervention; $t(25) = 3.3$, $p = .003$, $d = .39$.There was no significant difference in means between the healthy controls at baseline [1208 (*SD* = 157) mm^3] and the exercise participants post intervention [1206 (*SD* = 169) mm^3]; $t(53) = -1.2$, $p = .125$, $d = .01$.

4.6 Lifestyle Measures

A summary of the results of the lifestyle scores is presented in **Table 11** and **Figure 10.** Lifestyle measures were normally distributed at baseline and post intervention.

4.6.1 Sleep

The mean number of sleep hours was [7.4 (*SD* = 1.6)] at baseline and [8.0 (*SD* = 1.2)] post intervention. There was a significant increase in sleep hours after the intervention; $t(39) = -2.2$, $p = .03$, $d = .36$. The mean rating of sleep quality was [6.6 (*SD* = 2.1)] at baseline and [7.2 (SD = 1.8)] post intervention. There was a significant increase in sleep quality reported after the intervention; $t(39) = -2.6$, $p = .013$, $d = .41$.

4.6.2 Diet

The mean rating of diet health was [6.0 (*SD* = 2.0)] at baseline and [6.6 (*SD* = 1.6)] post intervention. There was a significant increase in rating of diet health; $t(39) = -2.1$, $p = .044$, $d = .33$.

4.6.3 Exercise Enjoyment

The mean rating of exercise enjoyment was [6.1 (*SD* = 2.0)] at baseline and [8.0 (*SD* = 1.8)] post intervention. There was a significant increase in rating of exercise enjoyment; $t(39) = -7.2$, $p < .0001$, $d = 1.13$.

4.7 Relationship between Change in Hippocampal Volume and Change in Other Variables

Further analyses were conducted to test for significant relations between changes in hippocampal volume and other variables. A change in aerobic fitness was significantly correlated to a change in right hippocampal volume; $r(24) = .499$, $p = .009$ and a change in right anterior hippocampal volume; $r(24) = .459$, $p = .018$**. Figure 8** and **Figure 9** depict these correlations respectively. There was no significant correlation of change in aerobic fitness with a change in left hippocampal volume; $r(24) = .214$, $p = .291$, left anterior hippocampal volume; $r(24) = .268$, $p = .186$, left posterior hippocampal volume; $r(24) = -.199$, $p = .330$, nor a change in right posterior hippocampal volume; ; $r(24) = .388$, $p = .050$.

4.8 Categorical Comparisons

Exploratory analyses were conducted to determine whether there were significant differences in study variables between participants when categorized according to differing stages, level of attendance, gender, medication and age.

4.8.1 Stage Comparison

Descriptives of the sample and clinical comparisons based on stage are summarized in **Table 13**. There were no significant differences between Stage 2 and Stage 3 participants in terms of age; $t(39) = -1.5$, $p = .132$, $d = .50$, attendance; ; $t(39)= -.8$, $p = .404$, $d = .27$, gender; X^2 $(1, N = 41) = .05$, p = .823, $\varphi = .04$, or use of medication; X^2 $(1, N = 41) = .25$, p = .619, $\varphi = .08$.

With regard to clinical symptoms, there were no significant differences between stages in depression at baseline; $t(39) = -1.8$, $p = .079$, $d = .59$, anxiety post intervention;

$t(39) = -1.6$, $p = .127$, $d = .50$, distress post intervention; $t(38) = -.1$, $p = .943$, $d = .02$, depression post intervention; $t(39) = -1.0$, $p = .307$, $d = .31$, and change in depression; $t(39) = .8$, $p = .830$, $d = .26$.

There were, however, significant differences in several other variables. Stage 3 participants had a significantly higher SIAS score than Stage 2 participants at baseline; $t(39) = -3.2$, $p = .013$, $d = 1.05$. Stage 3 participants also had a significantly greater change in SIAS score than Stage 2 participants; $t(39) = 2.6$, $p = .013$, $d = .85$. Additionally, Stage 3 participants had a significantly higher K-10 Distress score than Stage 2 participants at baseline; $t(38) = -2.8$, $p = .008$, $d = .93$. Stage 3 participants also had a significantly greater change in K-10 Distress Scale; $t(38) = 2.7$, $p = .011$, $d = .87$, which was not unexpected given that their higher baseline scores allowed greater potential for improvement.

Regarding SOPS measures, the Wilcoxon Signed-ranks test was used to analyze dependent variables and the Mann-Whitney test was used for independent variables. There was no significant reduction in APS following the exercise intervention in Stage 3; $z = -1.0$, $p = .322$. The sample size was too small to detect significance in Stage 2 participants. Positive symptoms were greater for Stage 3 participants at baseline (Md = 5.5) than Stage 2 participants (Md = 0.5), $U = 67.5$, $p = .006$. Similarly, Stage 3 participants post intervention had higher APS (Md = 5.5) than Stage 2 (Md = 0.0), U = 89.0, $p = .005$. There was no significant reduction in negative symptoms following the exercise intervention in Stage 2; $z = -1.3$, $p = .208$ and a significant reduction in Stage 3; $z = -2.0$, $p = .043$. Negative symptoms were greater for Stage 3 participants at baseline (Md = 6.0) than Stage 2 participants (Md = 2.0), $U = 112$, $p = .028$. Stage 3 participants post intervention had non-significantly higher negative symptoms (*Md* = 3.0) than Stage 2 (*Md* = 1.5), *U* = 134.5, *p* = .116.

There was no significant reduction in disorganization symptoms following the exercise intervention in Stage 3; *z* = -.8, *p* = .423. The sample size was too small to detect significance in Stage 2 participants. Disorganization symptoms were significantly greater in Stage 3 participants at baseline (*Md* = 2.0) than Stage 2 (*Md* = 1.0), *U* = 91, *p* = .006. Post intervention there were no significant differences between Stage 3 (*Md* = 1.0) compared with Stage 2 participants (*Md* = 1.0), *U* = 127, *p* = .075. There was a significant reduction in general symptoms following the exercise intervention in Stage 2; *z* = -3.0, *p* = .003 and Stage 3; *z* = -3.3, *p* < .001. General symptoms were greater for Stage 3 participants at baseline (*Md* = 8.0) than Stage 2 participants (*Md* = 5.0), *U* = 93, *p* = .006. Stage 3 participants post intervention had higher general symptoms (*Md* = 5.0) than Stage 2 (*Md* = 1.5), *U* = 89.5, *p* = .005.

Stage 2 participants had significantly higher Aerobic Fitness than Stage 3 participants at baseline; *t*(39) = 2.6, *p* = .012, *d* = .80, and post intervention; *t*(39) = 3.4, *p* = .001, *d* = 1.09.

4.8.2 Attendance Comparison

Differences in the sample based on attendance are summarized in **Table 14**. There were no significant differences between participants who attended less than 50% of the sessions and those who attended ≥50% in terms of age; *t*(39) = -.1, *p* = .958, *d* = .11, gender; X^2 (1, *N* = 41) = .14, *p* = .713, φ = .18, stage; X^2 (1, *N* = 41) = 1.41, *p* = .236, φ = .18 or use of medication; X^2 (1, *N* = 41) = .23, *p* = .631, φ = .08. There was a greater change in aerobic fitness in those participants who attended ≥50% of the sessions as compared to those who attended < 50%; $t(39) = -2.0$, $p = .049$, $d = .67$.

There were no differences in any clinical symptoms except a significantly greater BDI score at baseline in those participants who attended less than 50% of the sessions than those who attended ≥50%; $t(39) = 2.6$, $p = .013$, $d = .90$.

4.8.3 Gender Comparison

There were no significant differences between male and female participants in terms of age; $t(39) = -.1$, $p = .879$, $d = .11$, attendance; $t(39) = 1.0$, $p = .336$, $d = .36$, stage; X^2 (1, $N = 41$) = .05, $p = .823$, $\varphi = .04$ or use of medication; X^2 (1, $N = 41$) = .23, $p = .631$, $\varphi = .08$. Females had significantly lower Aerobic Fitness than males post intervention; $t(39) = 2.2$, $p = .036$, $d = .69$.

In relation to clinical symptoms, at baseline females had higher distress; $t(39) = -3.3$, $p = .002$, $d = 1.31$, anxiety; $t(39) = -2.3$, $p = .029$, $d = .82$, and depression; $t(39) = -2.1$, $p = .041$, $d = .77$. Post intervention, females remained significantly higher than males in anxiety; $t(39) = -2.7$, $p = .009$, $d = 1.04$.

4.8.4 Medication Comparison

There were no significant differences between participants taking or not taking medication in terms of age; $t(39) = -.34$, $p = .736$, $d = .11$, attendance; $t(39) = -1.31$, $p = .309$, $d = .33$, gender; X^2 (1, $N = 41$) = .12, $p = .728$, $\varphi = .05$ and stage; X^2 (1, $N = 41$) = 2.5, $p = .115$, $\varphi = .25$. No other study variables showed significance between those taking and not taking medication.

4.8.5 Age Comparison

There were no significant differences between participants <16 and those ≥16 years of age in terms of attendance; $t(39) = .2$, $p = .879$, $d = .05$, gender; X^2 (1, $N = 41$) = .14, $p = .712$, $\varphi = .14$, stage; X^2 (1, $N = 41$) = .54, $p = .460$, $\varphi = .11$ or use of medication; X^2 (1, $N = 41$) = 1.75, $p = .185$, $\varphi = .21$. In terms of clinical symptoms, the only variable that revealed a significant difference were participants ≥16 years of age having a significantly greater decrease in BDI scores; $t(38) = -3.0$, $p = .005$, $d = 1.01$.

5 DISCUSSION

5.1 Feasibility

The exclusion criterion in this study included engaging in vigorous physical activity for 60 minutes at least once a week was particularly lenient, being below the recommended 2011 guidelines set forth by the Canadian Society for Exercise Physiology (CSEP) (Trembley et al., 2011). According to results from a 2014 report card on physical activity for children and youth, only 5% of school-aged children and youth in Canada met physical activity requirements (Gray, et al., 2014). Comparable to this report, only 9% of initially eligible participants in this study were excluded due to being too active. Not only does this demonstrate that the sedentary lifestyle of this sample is representative of the general population, it implies more attention is needed to address this age group and its failure to meet even the minimum exercise recommendations.

Grounds for declining participation and lack of commencement varied with the majority voicing lack of interest. Perhaps in future studies further questioning to elucidate why the lack or loss of interest in participation may reveal barriers that are potentially workable. Similarly, inquiring what would motivate the youth to enroll would likely be valuable and potentially feasible to accommodate.

The 93% retention of study participants is very encouraging considering that the non-adherence to treatment with pharmacological interventions, such as antidepressants, is common (Pampallona, 2002). Additionally, in contrast to the poor adherence reported in prior research of exercise and mental illness (Vancampfort et al., 2015), this study demonstrated a high level of engagement. Participants were very adherent, far surpassing the exercise minimum of 75 minutes of vigorous intensity exercise per week as recommended in the CSEP 2011 guidelines (Trembley et al., 2011). The three participants that left the program and failed to complete the post intervention assessments could no longer be reached to determine their reason for discontinuing.

Attendance in the present study averaged between two and three times per week. This is consistent with other reviews in depression (Perraton et al., 2010; Stanton & Reabourn, 2014). Previous research has reported that youth at clinical high risk demonstrate more barriers related to motivation as compared to healthy controls (Newberry, Dean, Sayyah, & Mittal, 2018). Similarly, participants in the present study who reported higher baseline depression scores were more likely to attend less than 50% of the sessions. Focusing on motivation as both a recruitment and retention strategy may improve commitment to treatment. All of the exercise sessions were supervised with program delivery ranging from private, to semi-private to group training depending on the day. Although individualized training has been shown to be effective in previous studies of mental illness such as first-episode psychosis (Firth et al., 2016), group training likely helped with adherence, as social connections were made.

Achieving higher 'doses' of exercise may be more feasible by increasing the duration of each exercise session rather than increasing to a higher frequency per week. There is likely an inverted U relation with exercise and mental health; namely, more is not necessarily better beyond an individual's limits. Indeed, in a recent large cross-sectional study of 1.2 million people in the USA it was reported exercising more than twenty-three times per month or longer than ninety minutes per session was associated with worse mental health (Chekroud et al., 2018).

5.2 Clinical

Anxiety and depressive symptoms, as well as overall general symptoms, in particular intolerance to normal stress, were significantly reduced over the course of the study. Such results are consistent with previous research in mental illness and were expected given that the mental health benefits of exercise are more prominent in people suffering from anxiety and depression (Wergner et al., 2014). Systematic reviews similarly confirm that moderate to vigorous exercise reduces positive and negative symptoms in schizophrenia (Dauwan et al., 2016; Firth et al., 2015). Both positive and negative symptoms did decrease in this study cohort, albeit positive symptoms did not diminish significantly. However, these symptoms were in the normal range at baseline; therefore, a large change was not anticipated. Disorganization symptoms were unchanged, but similarly, were barely apparent at baseline.

Stress is a precipitating factor in susceptibility and exacerbation of mental health issues associated with reduced well-being and mental health (Hallam, Bilsborough & de Courten, 2018). The overall beneficial effects of exercise on general symptoms are likely multifactorial with purported explanatory theories being both physiological, as well as psychological given that the stress response is an outcome of both real and/or perceived physiological and psychological stressors. Stress is, however, highly responsive to exercise.

Most commonly cited physiological mechanisms involve: the HPA axis (Anderson & Shivakumar, 2013; Droste et al., 2003; Duclos & Tabrin, 2016; Zhu et al., 2014; Zschucke et al., 2015), the autonomic nervous system (Guiraud et al., 2013; Hepburn et al., 2005; Martikainen et al., 2013; Rimmele et al., 2009; Routledge et al., 2010), endorphins (Goldfarb, et al., 1987; Harte, Eifert, & Smith, 1995), endocannabinoids (Dietrich & McDaniel, 2004; Heyman et al., 2012), and neurotransmitters (Chen, et al., 2017; Maddock, Casazza, Fernandez, & Maddock, 2016). All of the aforementioned physiological components may be contributing to the observed results in this study, however each would require corroboration with their own specific testing.

From a psychological perspective, researchers have postulated that physical activity provides a mastery experience that leads to self-efficacy, which in turn lowers anxiety and stress reactivity (Netz et al., 2005). Along the same lines, physical fitness is linked to positive self-esteem and those with greater confidence are less prone to succumbing to depressive behavior (Chen et al., 2015). Such positive experiences with exercise feasibly contribute to the mood elevating capacity of exercise. In the present study, and consistent with prior research showing improvements in mood after acute and chronic exercise (Netz et al., 2005; Rimmele et al., 2009; Salmon, 2001), dysphoric mood was significantly reduced post-intervention.

When comparing participants based on Stage of Risk, not surprisingly, Stage 3 participants reported more symptoms of distress, anxiety, and overall prodromal symptoms at baseline than those in Stage 2. This substantiates the appropriateness of their classification. The greater reduction in symptoms for Stage 3 participants may have been due to there being more room for improvement.

Stage 3 participants had worse cardiorespiratory fitness than Stage 2. It is well documented that individuals with SMI have significantly impaired cardiorespiratory fitness in comparison to age and sex-matched healthy controls (Vancampfort et al., 2017). The current results reveal, even at a young age and prior to a formal diagnosis of SMI, worse symptoms are associated with reduced cardiorespiratory fitness. Very encouragingly, symptoms did not preclude significant aerobic fitness gains in either stage.

5.3 Cognition

Cognitive measures did not change after the exercise intervention. While working memory is often affected in mental illness, this sample demonstrated scores that were in the normal range. Although limited, there is some evidence aerobic exercise may lead to improvements in select cognitive tasks in healthy young adults (Hansen et al., 2004; Kamijo & Takeda, 2010), while other studies have reported working memory may remain unaffected (Stroth et al., 2010). Much of the research demonstrating cognitive gains after exercise has been conducted on pre-adolescent children (Chaddock et al., 2010) and older adults (Erickson et al. 2011), both of which characteristically exhibit great potential for enhancement. This cohort was not preselected based on poor cognitive performance, hence an improvement was not to be expected once it was realized there were no major shortfalls at baseline. The largest benefits of physical activity occur with tasks that require the greatest executive control (Colombe & Kramer, 2003). Therefore, the cognitive tasks chosen may not have been taxing enough to demonstrate any effects. The battery of cognitive tests could be expanded to detect changes in other domains besides working memory.

5.4 Physical Health

It is well documented that those diagnosed with mental illness are commonly less active than the general population (Soundy et al., 2013), putting them at further risk of disease such as obesity and other cardiometabolic disorders. Exposing participants to a positive exercise environment and having them experience the associated physical benefits may improve physical and mental resiliency and curtail risk of such diseases. These individuals may also be more apt to continue or re-engage in fitness endeavors after achieving ameliorations in physical health. Several facets of the participants' physical health in the present study improved.

Both systolic and diastolic blood pressure were found to be in the healthy ranges and decreased just slightly over the duration. A comprehensive review (Alpert & Wilmore, 1994) and meta-analysis (Kelley & Kelley, 2003) indicated no association between physical activity and blood pressure reduction in normotensive youth. While there is no need to reduce blood pressure in this normotensive cohort, the measurement was administered as a standard indicator of physical health.

Body composition significantly improved, reflecting a decrease in body fat percentage and approaching healthier ranges. Adiposity is generally considered as a state of low-grade inflammation (Das, 2001; Juge-Aubry Henrichot, & Meier, 2005); therefore, a reduction in body fat may be reflecting a decrease in inflammation.

Aerobic fitness improved markedly after the intervention. Participants were largely sedentary prior to the study; thus, significant improvements in aerobic fitness were anticipated. Systematic reviews and meta-analyses on cardiorespiratory fitness and mental illness reported that interventions with high intensity (greater than 75% Vo2max) and frequency (3 or more times per week), as well as qualified supervision, were effective at improving fitness (Rethorst, Wipfli & Landers, 2009; Vancompfort et al., 2017). While the exercise protocol in the current study was based on recommendations by the CSEP, other studies have varied in their protocol, hence explaining heterogeneity in effect sizes (Herring et al., 2010; Herring et al. 2012; Krogh et al., 2011). Exercise dose, which includes frequency, intensity, session length, and program duration, comprises parameters crucial in determining recommendations for mental health benefits. 30 minutes of daily moderate physical activity appears to be feasible for individuals with serious mental illness (Gorczynski, P., & Faulkneer, G., 2010). In the treatment of depression, the most successful protocols included a minimum of 30 minutes at 60-80% of maximum heart rate three times per week for at least eight weeks (Perraton, Kumar, & Machotka, 2010). In a meta-analysis examining the effect of dose, no linear relationship was found for depression (Rethorst, Wipfli, & Landers, 2009). In studies that compared different doses, it is suggested that higher doses are more effective than lower doses (Dunn et al., 2005; Legrand & Heuze, 2007; Singh et al., 2005; Trivedi et al., 2011). The present study used intensities that would be comparatively higher than most previous studies in depression, for example. In such studies, there are sizeable variations in intensity ranges from patient-preferred (Callaghan et al., 2011) to 75% of VO2max (Chu et al., 2009). A systematic review of exercise for anxiety disorders concluded both aerobic and anaerobic exercise appears to reduce anxiety symptoms (Jayakody, Gunadasa, & Hosker, 2014). Garber et al., highlight the further value of more vigorous exercise in healthy populations (2011), and based on favorable results presently achieved, there is some evidence higher intensities are well tolerated in youth at risk for SMI.

5.5 Neuroimaging

Hippocampal volumes are usually reported to be smaller in people who have mental illness and may eventually serve as a measurable marker of vulnerability and brain health. Youth in this study had significantly lower hippocampal volumes bilaterally in comparison to the healthy controls at baseline. This finding is consistent with previous research reporting that the hippocampal structure and its connections are impaired prior to the onset of psychosis (Bernard, Orr & Mittal, 2015; Dean et al., 2015). Children who have experienced early life adversity have smaller hippocampal volumes and are more likely to have a mental illness later on in life (MacQueen & Frodl, 2011; Dahmen et al., 2018). These smaller volumes may characterize a vulnerability to mental illness and also represent pathophysiological processes that have already taken place. A recent cross-sectional study on adolescent depression reported that small hippocampal volume was at least partly a result of early-life stress rather than the diagnosis of depression itself (Redlich et al., 2018). Ongoing stressors presumably further negatively impact hippocampal volumes, as seen in a chronic course of depression (Bell-McGinty et al., 2002; Videbech & Ravnkilde, 2004; Frodl et al., 2008). Regardless of the etiology, the fact that there are measurable changes in important brain regions highlights the need for early intervention when youth have been exposed to significant adversity.

After the intervention, the left hippocampus remained smaller than the controls. The right hippocampus normalized, increasing in volume to show no significant difference with the healthy controls post intervention. Asymmetrical volume increases as such have previously been found. In a meta-analysis by Li et al., the pooled results of seven studies revealed aerobic exercise significantly increased right hippocampal volume and trended towards improvements in the left hippocampus. The authors suggested aerobic exercise might have positive effects on the right hippocampus and potentially beneficial overall effects on other parts of the hippocampus (Li et al., 2017). Previous studies have also reported hippocampal plasticity centered on the hippocampal head (Erickson et al., 2011; Sagi et al., 2012), hence some recent studies have focused solely on the anterior hippocampus (Thomas et al., 2016). In the present study, both the anterior and posterior right hippocampal volume increased, albeit more so in the anterior portion. A positive correlation was noted between both the right whole and right anterior hippocampus and a change in aerobic fitness. These results are similar to a cross-sectional study, which reported that the number of minutes of exercise per week was significantly correlated with hippocampal volume, specifically within the right anterior hippocampus (Killgore, Olsen & Weber, 2013). Subfield analyses failed to uncover any underlying regions within either hippocampus that distinctly differed in responsiveness.

In relation to laterality in the hippocampus, beyond that of cognition (Burgess, Maguire & O'Keefe, 2002), and pertinent to the results obtained in the current study, a negative relation between chronic life stress and right hippocampal volumes has been reported (Gianaros et al., 2007). Furthermore, Agroskin, Klackl & Jonas (2014) reported a positive association between self-esteem and grey matter volume in several laterally distinct regions including the right hippocampus. Such a hippocampal-self-esteem relationship may be relevant to understanding the results of this study, as there is evidence that exercise boosts self-esteem (Joseph, Royse, Benitez & Pekmezi, 2014; Legrand, 2014; Park, Han, & Kang, 2014). Additionally, greater rightward hippocampal asymmetry has been noted in healthy controls versus those suffering from major depression (Xia et al., 2004) and those with subjective cognitive decline and mild cognitive impairment (Yue et al., 2018). These authors even suggest such asymmetry may be a more sensitive biomarker than total volume. Rightward asymmetry in healthy individuals is purported to be principally due to the anterior hippocampus (Woolard & Heckers, 2012). There may be functional implications to such hemispheric asymmetry as in schizophrenia there is a decrease in volume of the anterior hippocampus (Pegues et al., 2003; Thoma et al., 2008) and a reduction in hippocampal asymmetry has been linked to that illness (Sun et al., 2017).

The anterior hippocampus has direct connections with the amygdalar nuclei (Duvernoy, 2005) and shares a pathway with the amygdala to the fusiform cortex (Smith et al., 2009). Functional connections include the ventral tegmental area and the shell of the nucleus accumbens (Haber & Knutson, 2010; Krebs et al., 2011). Resting state MRI studies have revealed functional connections to the amygdala, hypothalamus and antero-lateral temporal lobes (Poppenk & Moscovitch, 2011). These connections support motivational processing (Adolphs, 2008; Grabenhorst & Rolls, 2011; Krebs et al., 2011). Physical exercise activates these regions in the brain reward systems (Bothe et al., 2013) and may therefore underlie effects on the anterior hippocampus.

Moreover, greater aerobic capacity is positively correlated with grey matter density in the right anterior insular cortex (Peters et al., 2009), a structure that has direct connections to the anterior hippocampus. The insular cortex plays a role in cardiovascular control (Lanfranchi & Somers, 2002; Nagai, Hoshide, & Kario, 2010); therefore, the robust increase in cardiovascular fitness over the course of the exercise intervention may have preferentially affected these specific interconnected brain regions, although this is highly speculative.

5.6 Lifestyle Measures

5.6.1 Sleep

All categories of lifestyle measured significantly improved post intervention. Meta-analyses and systematic reviews report millions of adolescents worldwide achieve insufficient sleep, that is, less than 8 hours (Gradisar, Gardner & Dohnt, 2011). Obtaining less than 8 hours not only increases sleepiness during the day, but furthermore decreases motivation, mood, intelligence task scores (Gradisar, Terrill, Johnston & Douglas, 2008) and daytime functioning (Warner, Murray & Meyer, 2008). Conversely, increased sleep duration and quality have been associated with better school performance (Dewald, Meijer, Oort, Kerkhof, & Bogels, 2010). This cohort edged closer towards 8 hours of sleep per night post intervention, as well as reported significant improvements in sleep quality. These results are in line with a meta-analytic review reporting that regular exercise has small beneficial effects on total sleep time and moderate beneficial effects on sleep quality (Kredlow, Capozzoli, Hearon, Calkins & Otto, 2015). Physical activity (Chennaoui, Arnal, Sauvet & Leger, 2015) and adopting a lifestyle conducive to adequate sleep are crucial given that lack of sleep is detrimental to performance and healthy functioning (Roberts, Roberts, & Duong, 2009), although subject to multiple factors such as age, sex, and fitness level, etc. Research has reported improved sleep and psychological functioning with regular aerobic exercise in adolescents (Kalak et al., 2012). Youth with at-risk mental states engage in low amounts of physical activity and have poor sleep quality (Lederman, Rosenbaum, Maloney, Curtis, & Ward, 2017). Therefore, in particular, they are very likely stand to benefit from these auspicious effects. Future study may be able to incorporate sleep monitoring to more precisely investigate its role in exercise and mental health.

5.6.2 Diet

Subjective improvements in diet health just reached significance post intervention. Mood and behavior are inextricably related to diet and recent research has uncovered associations between dietary intake and the risk for the prevalence of mental illness such as depression (Lai et al., 2014; O'Neil et al., 2014; Psaltopoulou et al., 2013). A systematic review specifically involving children and adolescents found a relationship between a good quality diet and better mental health and some evidence for the reverse (O'Neil et al., 2014). In the present study, it is difficult to disentangle the role exercise plays in this relation and whether the better mood resulted in making healthier food choices or the healthier foods resulted in better moods. Health promoting activities often lead to other behavioral changes to potentially further improve outcomes (Hallam et al., 2018). Regardless, dietary choice highlights yet another modifiable lifestyle factor capable of positively impacting symptoms. Future research may attempt to isolate how diet and exercise alone may affect the mental symptoms in youth at risk.

5.6.3 Exercise Enjoyment

Significant improvement in the enjoyment of exercise post intervention is an important outcome potentially influencing future participation. In a study examining the exercise practices of youth at clinical high risk of psychosis, previous negative experiences with exercise are cited as a barrier in more than twice the number than that of healthy controls (Deighton & Addington, 2015). In this same study other barriers listed are both a lack of skills and knowledge of how to perform certain types of exercise. Perhaps knowledge and fitness gains acquired in the current study bolstered confidence and influenced the participant's perspectives. Perception of fitness has been cited an impediment to participation in a CHR sample (Newberry, Dean, Sayyah, & Mittal, 2018).

The resulting small group setting in the present study may have added to the overall enjoyment experienced. In a review of exercise and depression, both individual and group programs appeared to be successful in treatment (Stanton & Reaburn, 2014). Group participation and monetary compensation for parking may have heightened motivation among the participants and contributed to the overall favorable experiences reported.

6 SUMMARY

This pilot study suggests that moderate to high intensity aerobic exercise may be an effective intervention in reducing early symptoms of mental illness in at-risk youth. The study further provides support for the neuroprotective capacity of exercise on the hippocampus in youth at risk of SMI. These results are consistent with evidence that indicates that moderate to high intensity exercise can be beneficial in at-risk youth and should be recommended in the absence of contra-indications. A recent meta-analysis supports the notion that physical activity can reduce the risk of developing mental illness (Schuch et al., 2018), thus, further encouraging this method of intervention. Indeed, the National Institute for Health and Clinical Excellence (NICE) in the UK recommends that exercise be considered a first step in the treatment and management of people with persistent sub-threshold depressive symptoms or mild to moderate depression (NICE, 2010).

A randomized controlled trial is warranted to determine if the observed symptom reductions were attributable to the exercise intervention. Nevertheless, by reducing, or at a minimum, delaying symptoms of mental illness, valuable time and quality of life are preserved during crucial years of development. Interventions that effectively reduce symptoms, especially those experienced early on, may improve the likelihood of recovery and diminish the risk of future suffering from mental illness. As evidenced by the current study outcomes, it is apparent that exercise has potential as an intervention strategy. Some research suggests that physical activity and psychotherapy are equally effective (Raglin, 1990) and, more recently, exercise having greater effectiveness than problem-solving therapy in youth with mental health problems (Parker et al., 2016).

The most notable correlations were that of a change in aerobic fitness and hippocampal volume, suggesting that a strong physical stimulus induced morphological changes in the brain. Additionally, there was a correlation with a change in aerobic fitness and attendance, likely representing the anticipated dose-response relationship. There was no direct correlation between symptom improvement, change in aerobic fitness, attendance and hippocampal growth, presumably underscoring multiple determinants at play. New connections, improved friendships, teamwork, group participation and interpersonal support have all been shown to improve mental health (LaMontagne, et al., 2014). Restructuring the design of the study may help to reveal the degree to which social context and/or the physiological stimulus were responsible for symptom changes observed.

7 LIMITATIONS

Although the objective of this pilot study was to assess the feasibility and effects of aerobic exercise, due to the open-label design, numerous environmental factors may have led to the symptom improvements. Sixty-one percent of the participants were concurrently being treated pharmacologically, with the majority of them using anti-depressants. Although usage did not change over the duration of the study, there may have been benefits from the medication that should not be incorrectly interpreted as strictly from exercise. Medication did not appear to preclude any symptom improvements.

Caution must be taken in generalizing observed symptom changes to the greater population of youth at risk. Selection bias may have occurred as those enrolled may have had a better attitude towards exercise and would be more apt to prioritizing a healthy lifestyle.

Several measures were based on self-reports, thereby creating an inherent bias. Some measures may be objectified in future studies, e.g. actigraphy for sleep quality.

It is unknown whether observed changes persisted in this study sample once post intervention assessments were completed. Likewise, it is unknown whether participants continued to exercise at the end of the program. Compliance to some form of exercise regime is likely required for maintenance of benefits. More active individuals report greater ability to cope with stressors than less active peers (Bernstein & McNally, 2018; Craft, 2005; Kishida & Elavsky, 2015), therefore had participants reverted back to a sedentary lifestyle with a coincident worsening of symptoms, it points to the need for ongoing exercise as a coping strategy that may have helped manage their condition.

Assessments of aerobic fitness are inherently limited by one's motivation, which may bias results. Improvements may also be due to familiarity with the test procedure and the exertion required. Fear of fitness testing, or lack thereof, may skew results and may, to a degree, be misinterpreted as a change in physical capacity. Additionally, neither the participants, nor the lead researcher administering the fitness tests, were blinded: therefore, performance bias may have occurred.

The exercise protocol was based on perceived exertion and periodically monitored throughout the sessions. This limits the accuracy of determining the actual dose-response relationship and subsequent exercise prescription. The continuous use of heart rate monitors and activity trackers in future studies would help ensure that appropriate workloads were maintained and accounted for. Usage of such devices may also aid in motivation.

Careful delineation of the anterior and posterior hippocampus relies on judgment by the manual tracer. As technology progresses, higher resolution images and segmentation algorithms that differentiate the two segments will likely aid in this process. Hippocampal volumes are a coarse simplification devoid of full anatomical detail; therefore, advanced and more elaborate imaging technologies detecting molecular, cellular, and shape alterations may conceivably reveal the biological driver(s) and morphological components of these volume changes.

8 CONCLUSION & FUTURE DIRECTION

While symptoms may diminish through natural history, a growing body of evidence suggests that aerobic exercise and the subsequent improvements in physical health may reduce symptoms of mental illness. Aerobic exercise programs such as the one employed in this study offer preliminary support for its feasibility and inclusion as a sound intervention strategy for reducing symptoms and improving overall physical health, including brain health, in youth at risk for SMI.

The results, while preliminary, offer justification for randomized controlled trials with larger sample sizes to determine whether aerobic exercise promotes mental health and hippocampal plasticity in youth at-risk for SMI. There remain many unanswered questions related to the underlying biological mechanisms, the optimum dosing and components of the exercise training and the moderating factors associated with positive effects of aerobic exercise on mental health.

Despite strong adherence to the exercise intervention, many individuals that were introduced to the program lacked interest. Motivational interviewing at the outset, as well as done upon program completion, may offer valuable insight critical to future participation.

Attendance and fitness gains in groups proved to be much more effective than in those that exercised with fewer participants. Subsequent programs should be structured in a group format to reap the greatest benefits.

Including the use of activity tracking technologies in future research may help to determine actual behavioral changes including physical activity, sedentary time, sleep parameters, and further refine the optimal exercise prescription. Frequent symptom monitoring, e.g., every two weeks, would allow one to gain a better perspective of the trends and similarly, aid in the protocol refinement. Additionally, it may help the health care provider in advising participants when they may expect to experience overall symptom reduction.

More elaborate multimodal neuroimaging may elucidate mechanisms responsible for observed hippocampal changes. DTI, specifically investigating the fornix, cingulum and uncinate fasiculus, may reveal structural white matter contributions to hippocampal health. Spectroscopy, for example, examining change in N-acetylaspartate, a marker of neuronal integrity, may uncover changes at the cellular level. Arterial spin labeling, a neuroimaging technique that determines cerebral blood flow, may offer further insight to exercise-induced hippocampal changes.

1. TABLES

Table 1 Summary of Study Assessment Methods

Assessment	Measure/Software
Clinical	
Anxiety	Social Interaction Anxiety Scale (SIAS)
Depression	Beck's Depression Inventory-II
Attenuated psychotic symptoms	Scale of Prodromal Symtoms (SOPS)
Distress	K-10 Distress Scale
Health	
Blood pressure	Sphygmomanometer
Body weight	Scale
Body Composition	Calipers
Lifestyle	Self-report questionnaire
Fitness	
Aerobic Capacity	Cooper Assessment of Maximal Oxygen Uptake
Working Memory	
Verbal & Non-verbal	Letter Number Span & Spatial Span. Wechsler Memory Scale-Third Edition (WMS-III)
Neuroimaging	
Total Intracranial Volume	FSL 5.0.5 (www.fmrib.ox.ac.uk/fsl)
Total Hippocampal Volume	MultiTracer2, 3D ConvNets , ITK-SNAP
Hippocampal Subfield Segmentation	Freesurfer v6.0 (http://surfer.nmr.mgh.harvard.edu)

Table 2 Exclusion, Consented, and Retention Analysis

	Participants (n/N)	*Percentage (%)*
Exclusion	29/128	22.7
Consented	57/99	57.6
Retention	41/44	93.2

Table 3 Demographic Characteristics of Exercise Participants

Characteristic	Exercise Participants (n=41)
	M (SD)
Age (years)	17.7 (3.4)
	n (%)
Gender	
Female	29 (71)
Male	12 (29)
Race	
First Nations	0 (0.0)
Asian	6 (14.6)
Black	4 (9.8)
Caucasian	26 (63.4)
Southeast Asian	1 (2.4)
Central/South American	2 (4.9)
Interracial	2 (4.9)
Paternal Education	
High school or less	12 (29.3)
College or more	29 (70.7)
Maternal Education	
High school or less	8 (19.5)
College or more	33 (80.5)
Marital status	
Single/never married	39 (95.1)
Other	2 (4.9)
Current living arrangement	
Living with family	34 (82.9)
Living with partner	2 (4.9)
Living on own	2 (4.9)
Living with others	3 (7.3)
Current student	31 (75.6)
Current employment	
Full-time	4 (9.8)
Not full-time	37 (90.2)

Table 4 Clinical Scores

	Baseline (n=41)		Post-Intervention (n=41)		Paired Differences			
Assessment	***M (SD)***	**Range (Min - Max)**	***M (SD)***	**Range (Min - Max)**	***M (SD)***	***t(df)***	***p***	***d***
K-10[a]	21.3 (7.4)	(10-37)	20.6 (8.5)	(10-45)	1.9 (7.6)	-1.5(39)	.131	0.24
SIAS[b]	27.1 (17.0)	(2-60)	24.4 (17.3)	(5-61)	3.4 (9.2)	-2.3(40)	**.024***	0.37
BDI-II[c]	12.7 (9.5)	(1-35)	10.6 (11.4)	(0-46)	-3.3 (7.9)	-2.6(39)	**.012***	0.42

[a]K-10 Distress Scale. [b]Social Interaction Anxiety Scale. [c]Beck's Depression Inventory II. *d* = Cohen's d Effect Size
*$p < .05$; ** $p < .01$; *** $p < .001$

Table 5 Scale of Prodromal Symptom Scores

Symptoms	Baseline (N=40)		Post Intervention (N=40)		*Z*	*p*	*r*
	Median	***M (SD)***	***Median***	***M (SD)***			
Positive	4	4.6 (4.1)	1.5	3.3 (3.7)	-1.9	.062	.21
Negative	5	4.9 (3.7)	2	3.7 (5.0)	-2.4	**.015***	.27
N1	1	1.0 (1.3)	0	0.6 (1.2)	-2.2	**.032***	.34
N2	1	1.6 (1.3)	.5	1.3 (1.5)	-1.5	.134	.24
N3	0	0.2 (0.5)	0	0.2 (0.8)	-.41	.680	.12
N4	0	0.5 (0.7)	0	0.3 (0.8)	-1.3	.200	.20
N5	0	0.4 (0.9)	0	0.1 (0.4)	-2.2	**.027***	.35
N6	1	1.1 (1.3)	0	1.1 (1.7)	-.25	.805	.04
Disorganization	1	1.9 (1.7)	1	1.8 (2.4)	-.87	.386	.10
General	7	7.3 (3.4)	4	4.2 (3.3)	-4.4	**<.0001*** **	.50
G1	2.5	2.4 (1.4)	1	1.6 (1.6)	-2.7	**.008****	.41
G2	2	2.4 (1.3)	1	1.2 (1.3)	-4.0	**<.0001*** **	.63
G3	0	0.5 (0.9)	0	0.5 (0.8)	-.64	.949	.10
G4	2	2.0 (1.6)	.5	1.0 (1.2)	-3.5	**<.0001*** **	.56

N1=Social Anhedonia; N2=Avolition; N3=Expression of Emotion; N4=Experience of Emotions and Self; N5= Ideation Richness: N6= Occupation Functioning G1=Sleep Disturbance; G2=Dysphoric Mood; G3=Motor Disturbances; G4=Impaired Tolerance to Normal Stress. *$p < .05$; ** $p < .01$; *** $p < .001$. *r* = Effect size

Table 6 Cognition

	Baseline		Post-Intervention		Paired Differences			
Assessment	**(N=38) *M (SD)***	**Range (Min - Max)**	**(N=38) *M (SD)***	**Range (Min - Max)**	***M (SD)***	***t(df)***	***p***	***d***
FS	9.7 (1.2)	(7-12)	9.5 (2.2)	(4-13)	-.2 (1.6)	-0.2(37)	.552	.10
BS	8.0 (2.0)	(2-11)	8.4 (2.3)	(4-14)	0.0 (2.2)	0.0(37)	1.000	.00
LNS	15.1 (3.7)	(3-22)	15.3 (3.5)	(3-20)	.2 (2.5)	0.5(36)	.606	.06

FS; Forward Span. BS; Backward Span. LNS; Letter Number Span. $*p < .05$; $** p < .01$; $*** p < .001$. d = Cohen's d effect size

Table 7 Physical Health

	Baseline	Post-Intervention	Paired Differences			
Category	***M (SD)***	***M (SD)***	***M (SD)***	***t(df)***	***p***	***d***
Systolic BP (mmHg)	114.3 (10.9)	110.6 (10.7)	-3.7 (10.8)	-1.6(35)	.126	-
Diastolic BP (mmHg)	75.9 (10.6)	73.2 (8.7)	-2.7 (9.7)	-1.4(35)	.168	-
Body Composition (% Fat)	24.2 (7.8)	22.1 (7.7)	-2.1 (7.7)	-4.3(39)	**<.001*** **	.27
Aerobic Fitness (ml O2/kg^{-1}min^{-1})	20.0 (7.2)	31.0 (9.3)	9.0 (7.2)	7.9(39)	**<.0001*** **	1.25

$*p < .05$; $** p < .01$; $*** p < .001$

d = Cohen's d effect size

Table 8 Demographics of Neuroimaging Participants

Characteristic	Exercise Group (n=26)	Healthy Control (n=28)	Test Statistic	*p*	Effect Size
	M (SD)	***M (SD)***	***t***		***d***
Age (years)	17.8 (3.3)	18.8 (4.2)	-.9	.367	.26
Range	(12-24)	(12-25)			
	n (%)	***n (%)***	X^2		φ
Gender					
Female	18 (69.2)	18 (64.3)	.1	.700	.05
Male	8 (30.8)	10 (35.7)			
Current student	19 (73.2)	26 (92.9)	-		
Current employment					
Full-time	3 (11.5)	4 (14.3)	.1	.764	.04
Not full-time	23 (88.5)	24 (85.7)			
Marital status					
Single/never married	25 (96.2)	28 (100.0)	.3	.587	.07
Other	1 (3.8)	0 (0.0)			
Paternal Education					
High school or less	7 (26.9)	4 (14.3)	1.3	.249	.16
College or more	19 (73.1)	24 (85.7)			
Maternal Education					
High school or less	4 (15.4)	5 (17.9)	.1	.808	.03
College or more	22 (84.6)	23 (82.1)			
Race					***Cramer's V***
First Nations	0 (0.0)	1 (3.6)	.2	1.000	.38
Asian	5 (19.2)	5 (17.9)			
Black	2 (7.7)	0 (0.0)			
Caucasian	15 (57.7)	14 (50.0)			
Central/South American	2 (7.7)	0 (0.0)			
Middle Eastern	0 (0.0)	2 (7.1)			
Interracial	2 (7.7)	6 (21.4)			
Current living arrangement					
Living with family	21 (80.8)	24 (85.7)	.4	.946	.08
Living with partner	1 (3.8)	0 (0.00)			
Living on own	1 (3.8)	3 (10.7)			
Living with others	3 (7.32)	1 (3.6)			

Table 9 Neuroimaging Mean Volumes

Region	Baseline	Post Intervention	*t(df)*	*p*	*d*
	M (SD) **(N=26)**				
Intracranial Volume (mm^3)	2065425 (72703)	2089637 (59550)	1.7(25)	.10	.36
Left Hippocampus (mm^3) [%ICV]	2924 (333) [0.142]	2928 (396) [0.140]	.1(25)	.940	.01
Right Hippocampus (mm^3) [%ICV]	3028 (364) [0.147]	3144 (362) [0.150]	4.1(25)	**<.001*** **	.32
Left Anterior Hippocampus (mm^3) [%ICV]	1759 (289) [0.085]	1786 (315) [0.085]	1.2(25)	.241	.09
Left Posterior Hippocampus (mm^3) [%ICV]	1166 (181) [0.056]	1142 (209) [0.055]	-.9(25)	.364	.12
Right Anterior Hippocampus (mm^3) [%ICV]	1885 (286) [0.091]	1939 (285) [0.093]	3.7(25)	**.001** **	.19
Right Posterior Hippocampus (mm^3) [%ICV]	1143 (149) [0.055]	1206 (169) [0.057]	3.3(25)	**.003** **	.39

*$p < .05$; ** $p < .01$; *** $p < .001$

d = Cohen's d effect size

Table 10 Neuroimaging Comparison of Exercisers and Healthy Controls

Region		Exercisers (n=26)	Healthy Controls (n=28)	*t (df)*	*p*	*d*
		M (SD)				
Intracranial Volume (mm^3)	Baseline	2065425 (72703)	2073593 (49216)	-.5(52)	.628	.13
	Post Intervention	2089637 (59550)		-1.1(52)	.284	.29
Left Hippocampus (mm^3) [%ICV]	Baseline	2924 (333) [0.142]	3220 (339) [0.156]	-3.2(52)	**.002****	.88
	Post Intervention	2928 (396) [0.140]		-2.9(52)	**.005****	.79
Right Hippocampus (mm^3) [%ICV]	Baseline	3028 (364) [0.147]	3266 (337) [0.156]	-2.5(52)	**.016***	.68
	Post Intervention	3144 (362) [0.150]		-1.3(52)	.207	.35
Left Anterior Hippocampus (mm^3) [%ICV]	Baseline	1759 (289) [0.085]	1895 (256) [0.091]	-1.8(52)	.072	.50
	Post Intervention	1786 (315) [0.085]		-1.4(52)	.165	.38
Left Posterior Hippocampus (mm^3) [%ICV]	Baseline	1166 (181) [0.056]	1325 (215) [0.064]	-3.0(52)	**.005****	.80
	Post Intervention	1142 (209) [0.055]		-3.2(52)	**.002****	.86
Right Anterior Hippocampus (mm^3) [%ICV]	Baseline	1885 (286) [0.091]	2058 (262) [0.099]	-0.3(52)	.776	.63
	Post Intervention	1939 (285) [0.093]		-0.2(52)	.866	.43
Right Posterior Hippocampus (mm^3) [%ICV]	Baseline	1143 (149) [0.055]	1208 (157) [0.058]	-0.2(52)	.853	.42
	Post Intervention	1206 (169) [0.057]		-1.2(52)	.125	.01

p* < .05; ** *p* < .01; * *p*< .001

d = Cohen's d effect size

Table 11 Lifestyle Scores

	Baseline		Post-Intervention		Paired Differences			
Category	**(N=40) *M (SD)***	Range (Min - Max)	**(N=40) *M (SD)***	Range (Min - Max)	**(N=40) *M (SD)***	***t(df)***	***p***	***d***
Sleep Hours	7.4 (1.6)	(4-11)	8.0 (1.2)	(5.5-10)	.6 (1.6)	2.3(39)	**.03***	.36
Sleep Quality	6.6 (2.0)	(1-10)	7.2 (1.8)	(2-10)	.8 (1.9)	2.6(39)	**.013***	.41
Diet Health	6.0 (2.0)	(2-10)	6.6 (1.6)	(3-10)	.50 (1.5)	2.1(39)	**.044***	.33
Exercise Enjoyment	6.1 (2.0)	(2-10)	8.0 (1.8)	(3-10)	1.6 (1.4)	7.2(39)	**<.0001*****	1.14

p* < .05; ** *p* < .01; * *p* < .001

d = Cohen's d effect size

Table 12 Correlations of Attendance and Post Intervention Scores

	Attendance	Aerobic Fitness	Diet Health	Exercise Enjoyment
Attendance	-	**.366***	**.369***	**.355***
Aerobic Fitness		-	.296	**.453****
Diet Health			-	.254
Exercise Enjoyment				-

*$p < .05$; ** $p < .01$; *** $p < .001$

Table 13 Stage Comparison of Exercise Participants

Characteristic	Stage 2	Stage 3	Test Statistic	*p*	Effect size
	M (SD)	***M (SD)***	***t***		***d***
Age (years)	18.8 (3.3)	17.1 (3.5)	-1.5	.132	.50
Range (Min-Max)	(12-25)	(14-24)			
Attendance					
Sessions (%)	66.8 (23.8)	59.9 (26.5)	-.843	.404	.27
	(Min-Max)	*(Min-Max)*			
Range (%)	(14.6-97.9)	(8.3-100.0)			
	n(%)	***n(%)***	***X^2***		***φ***
	16 (39)	25 (61)			
Gender					
Female	11 (69)	18 (72)	.05	.823	.04
Male	5 (31)	7 (28)			
Medication					
No medication	7 (44)	9 (36)	.25	.619	.08
Medication	9 (56)	16 (64)			
Anti-depressant	9 (56.25)	10 (40.00)			
Anxiolytic	0 (0)	1 (4)			
Anti-psychotic	0 (0)	2 (8)			
Combination	0 (0)	3 (12)			
	M (SD)	***M (SD)***	***t(df)***		***d***
SIAS[b] Baseline	19.1 (14.2)	35.0 (16.3)	-3.2(39)	**.003****	1.05
K-10[a] Baseline	19.5 (6.0)	25.8 (7.5)	-2.8(38)	**.008****	.93
Aerobic Fitness Baseline	23.1 (8.4)	17.7 (4.4)	-2.6(38)	**.012***	.80
Aerobic Fitness Post Intervention	34.3 (9.0)	25.2 (7.7)	3.4(38)	**.001****	1.09
Change In SIAS	1.0 (7.7)	-6.2 (9.1)	2.6(39)	**.013***	.85
Change in K-10	1.8 (6.76)	-4.3 (7.21)	2.7(38)	**.011***	.87

*$p < .05$; ** $p < .01$; *** $p < .001$. *d* = Cohen's d effect size. *φ* = phi. *X2* = chi squared. K-10[a]; K-10 Distress Scale. SIAS[b]; Social Interaction Anxiety Scale

Table 14 Attendance Comparison of Exercise Participants

Characteristic	<50%	≥50%	Test Statistic	*p*	Effect size
	M (SD)	***M (SD)***	***t***		***d***
Age (years)	18.0 (3.7)	17.6 (3.4)	-.05	.958	.11
Range (Min-Max)	(13-25)	(12-24)			
	n(%)	***n(%)***	***X^2***		***φ***
	12 (39)	29 (61)			
Gender					
Female	8 (67)	21 (72)	.135	.713	.18
Male	4 (33)	8 (28)			
Stage					
Stage 2	3 (25)	13 (45)	1.41	.236	.18
Stage 3	9 (75)	16 (55)			
Medication					
No medication	4 (33)	12 (41)	.231	.631	.08
Medication	8 (67)	17 (59)			
Anti-depressant	7 (58)	12 (41)			
Anxiolytic	0 (0)	1 (3)			
Anti-psychotic	0 (0)	2 (7)			
Combination	1 (8)	2 (7)			
	M (SD)	***M (SD)***	***t(df)***		***d***
BDI-II Baseline	21.9 (9.6)	13.1 (10.1)	2.6(39)	**.013***	.90
Change in Aerobic Fitness	5.4 (8.5)	10.3 (6.3)	-2.0(38)	**.049***	.67

*$p < .05$; ** $p < .01$; *** $p < .001$. *d* = Cohen's d effect size. *φ* = phi. X^2 = chi squared

2. FIGURES

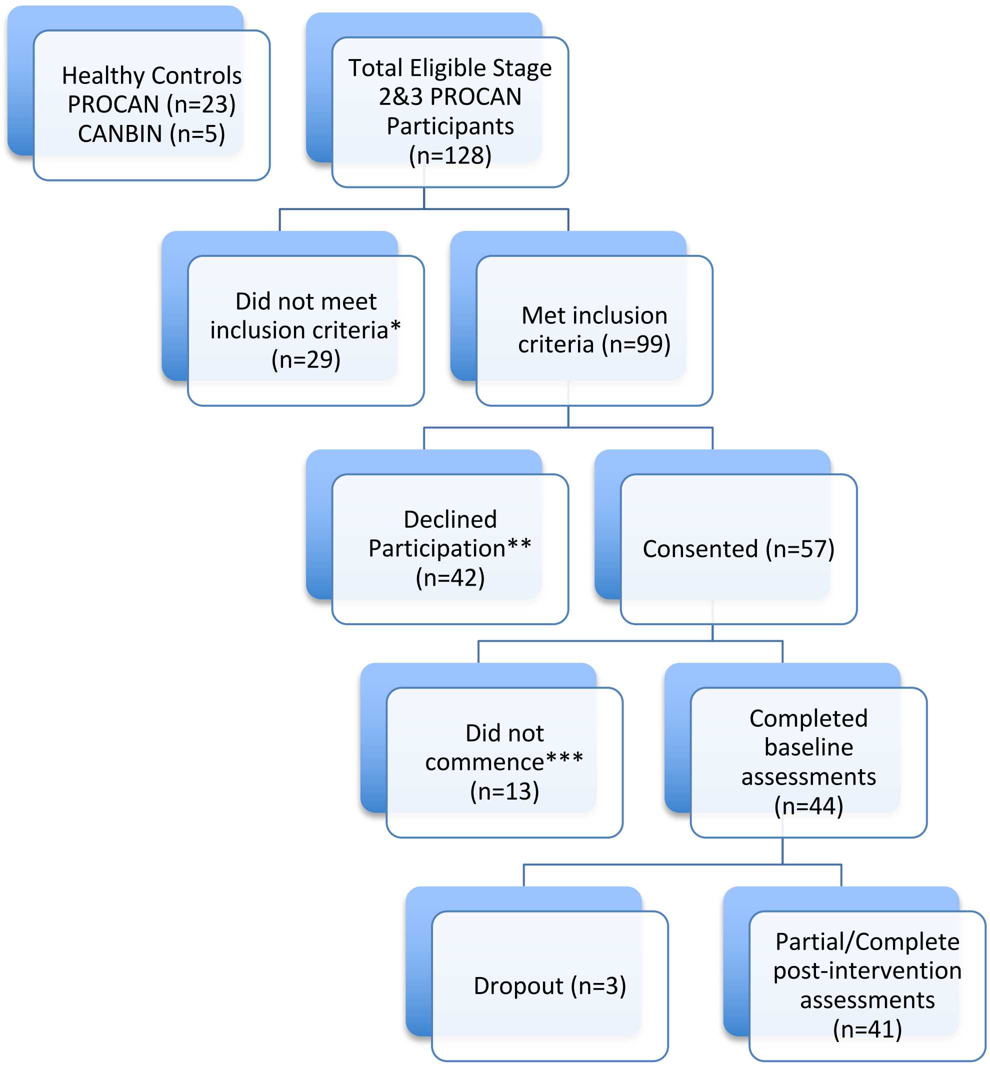

Figure 1. CONSORT Diagram of the Exercise Study

*Did not meet criteria; too active (n=11), in another group (n=18)

**Declined participation; live too far (n=6), time commitments (n=5), not interested (n=31)

***Did not commence; no longer interested (n=13)

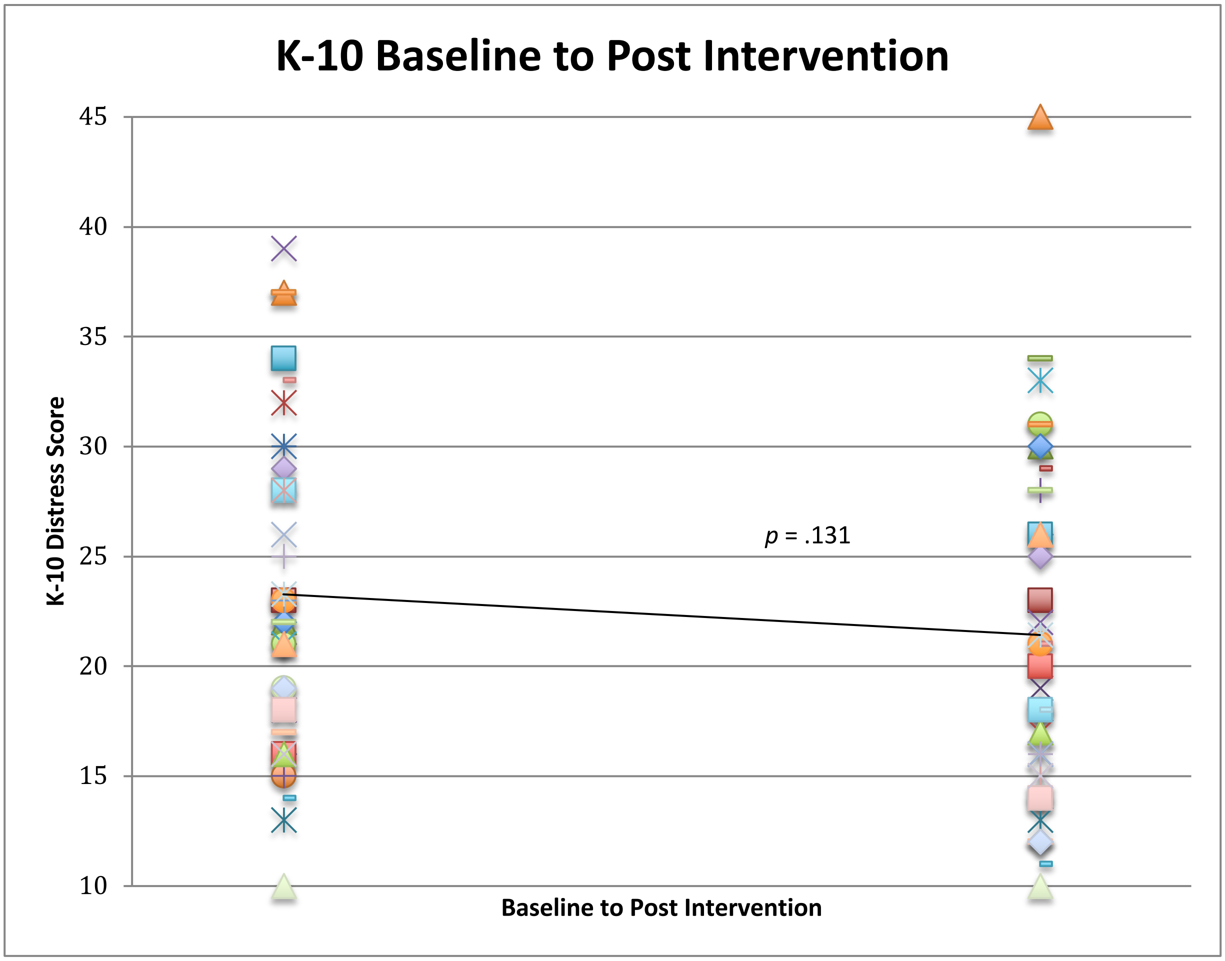

Figure 2. K-10 Distress Score Baseline to Post Intervention. **$*p < .05$; $**\ p < .01$; $***\ p < .001$**

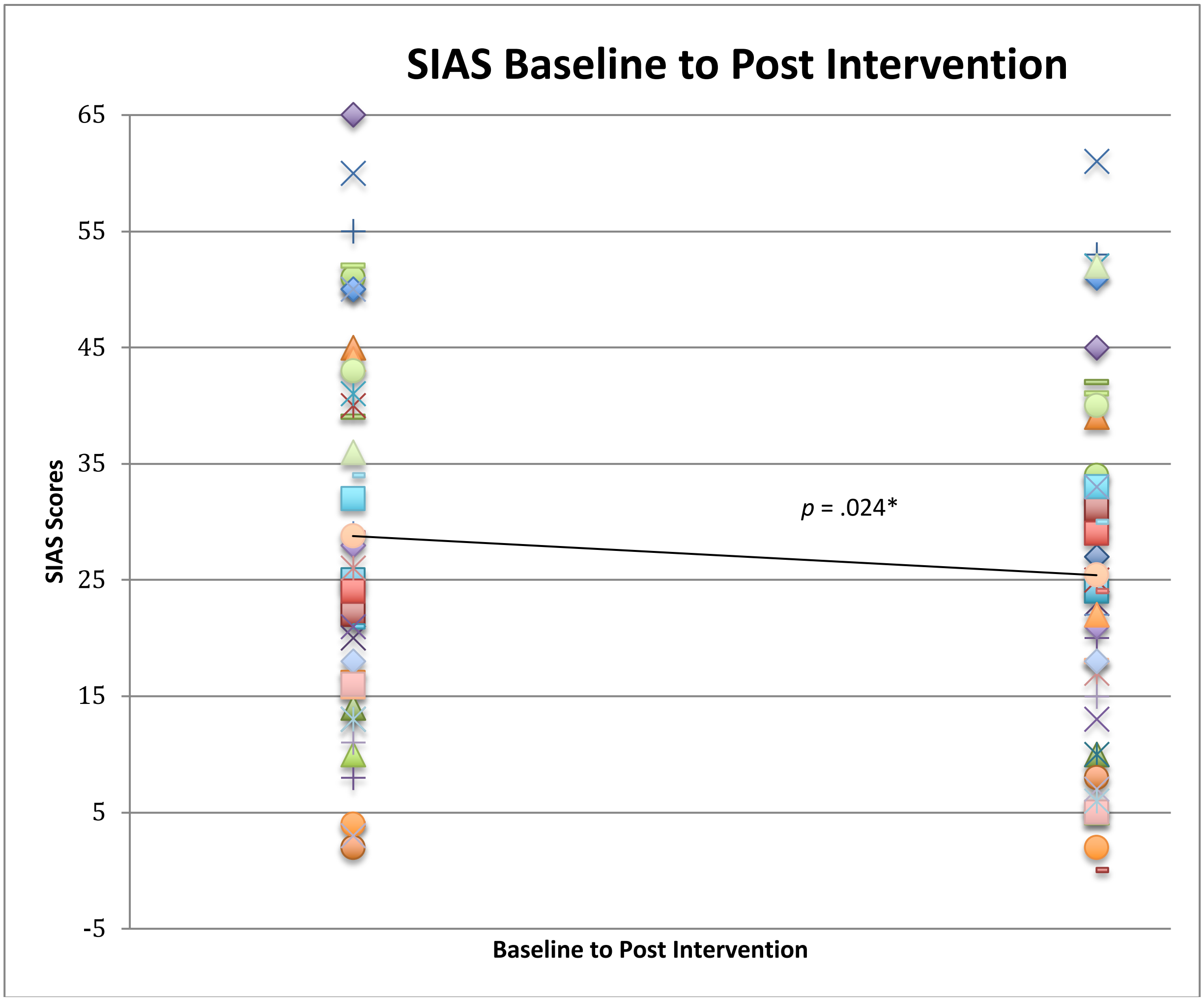

Figure 3. SIAS Baseline to Post Intervention. *$p < .05$; ** $p < .01$; *** $p < .001$

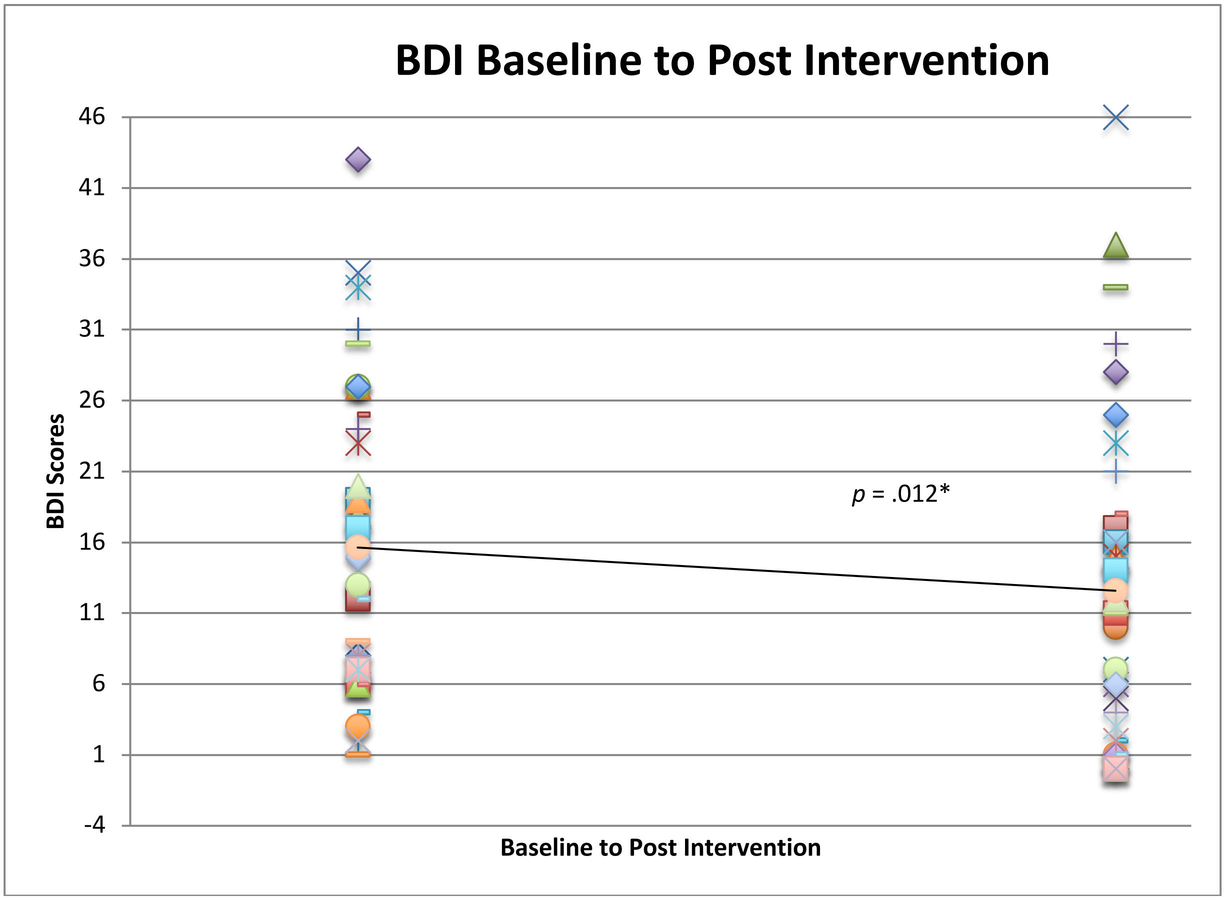

Figure 4. Beck's Depression Score Baseline to Post Intervention. *$p < .05$; ** $p < .01$; *** $p < .001$

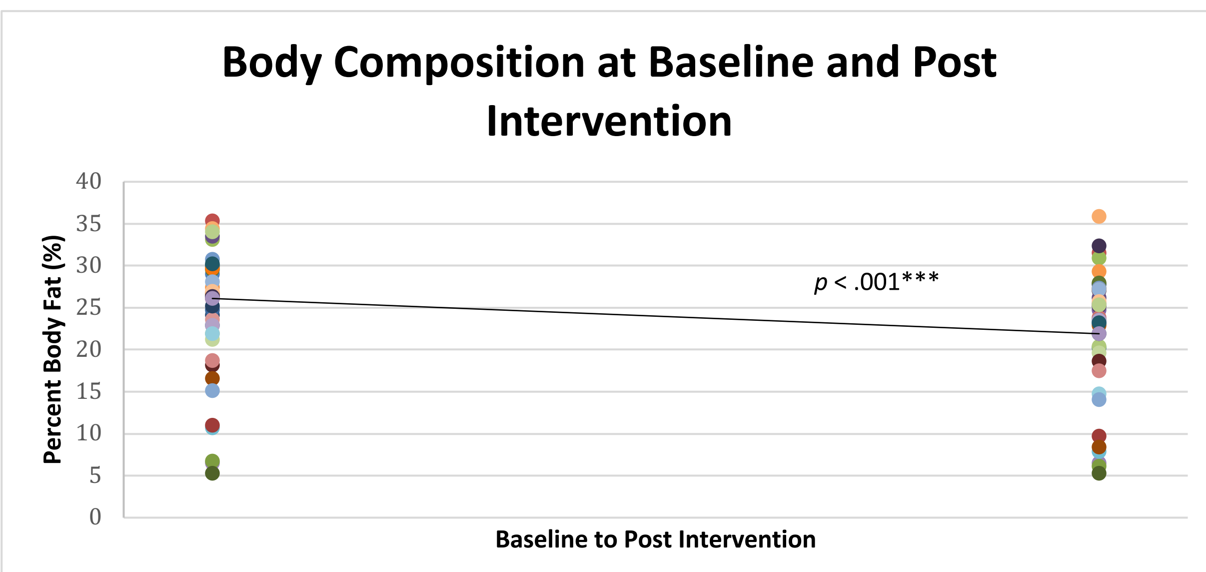

Figure 5. Body Composition Baseline to Post Intervention. *$p < .05$; ** $p < .01$; *** $p < .001$

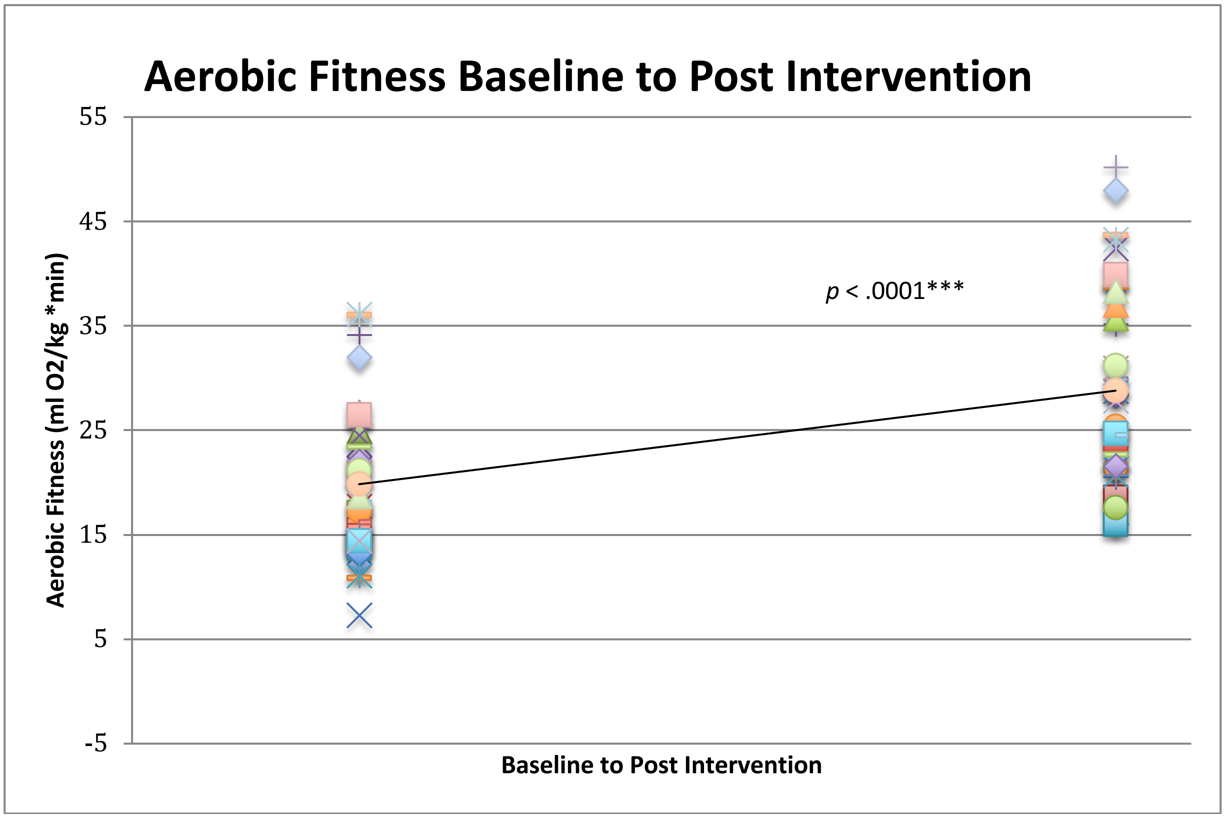

Figure 6. Aerobic Fitness Baseline to Post Intervention. *$p < .05$; ** $p < .01$; *** $p < .001$

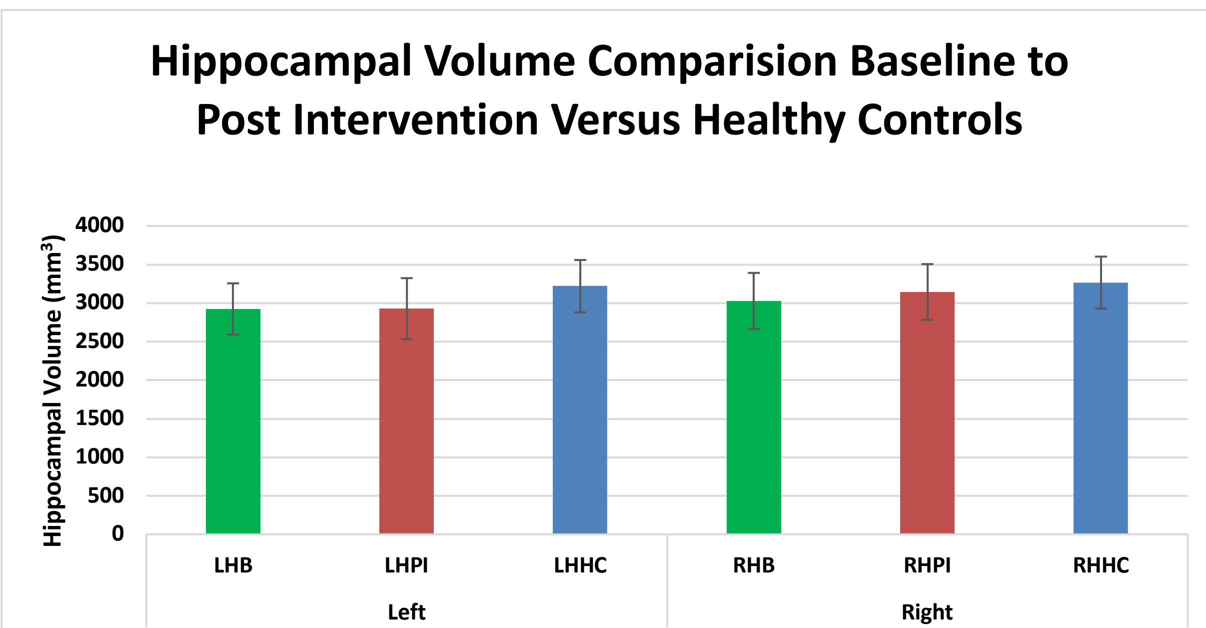

Figure 7. Hippocampal Volume Comparison Baseline to Post Intervention Versus Healthy Controls

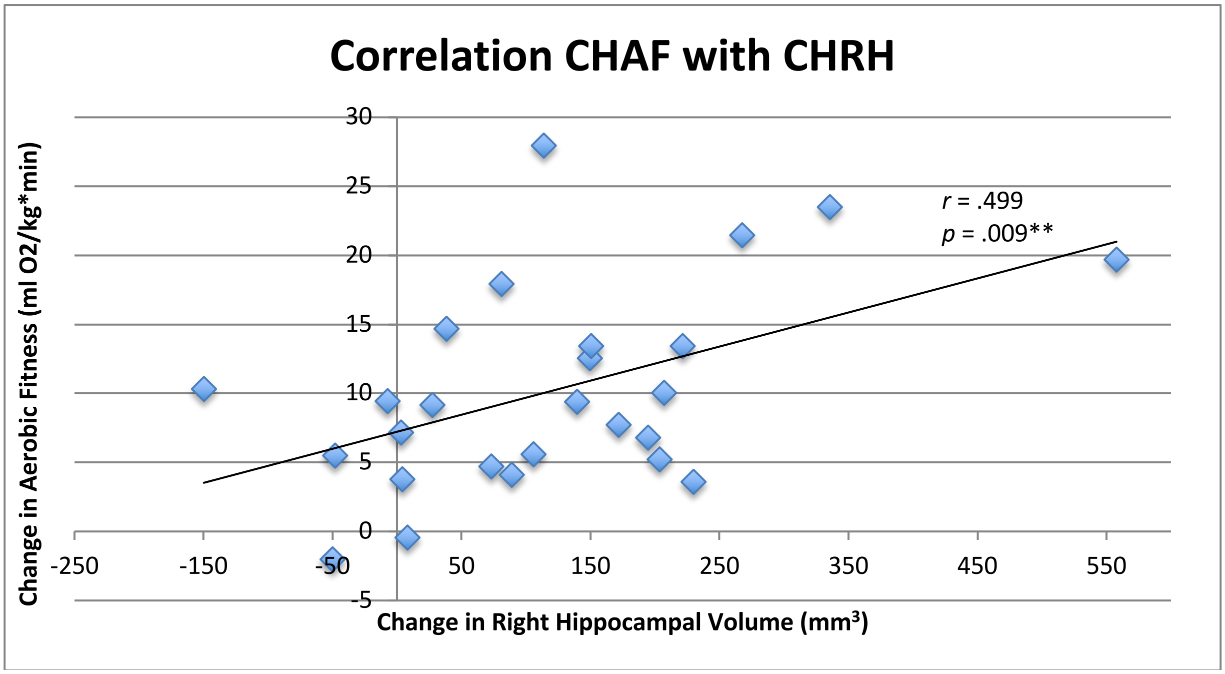

Figure 8. Correlation of CHAF with CHRH. CHAF; Change in Aerobic Fitness. CHRH; Change in Right Hippocampal Volume. **p* < .05; ** *p* < .01; *** *p* < .001. *r* = Pearson's Correlation Coefficient

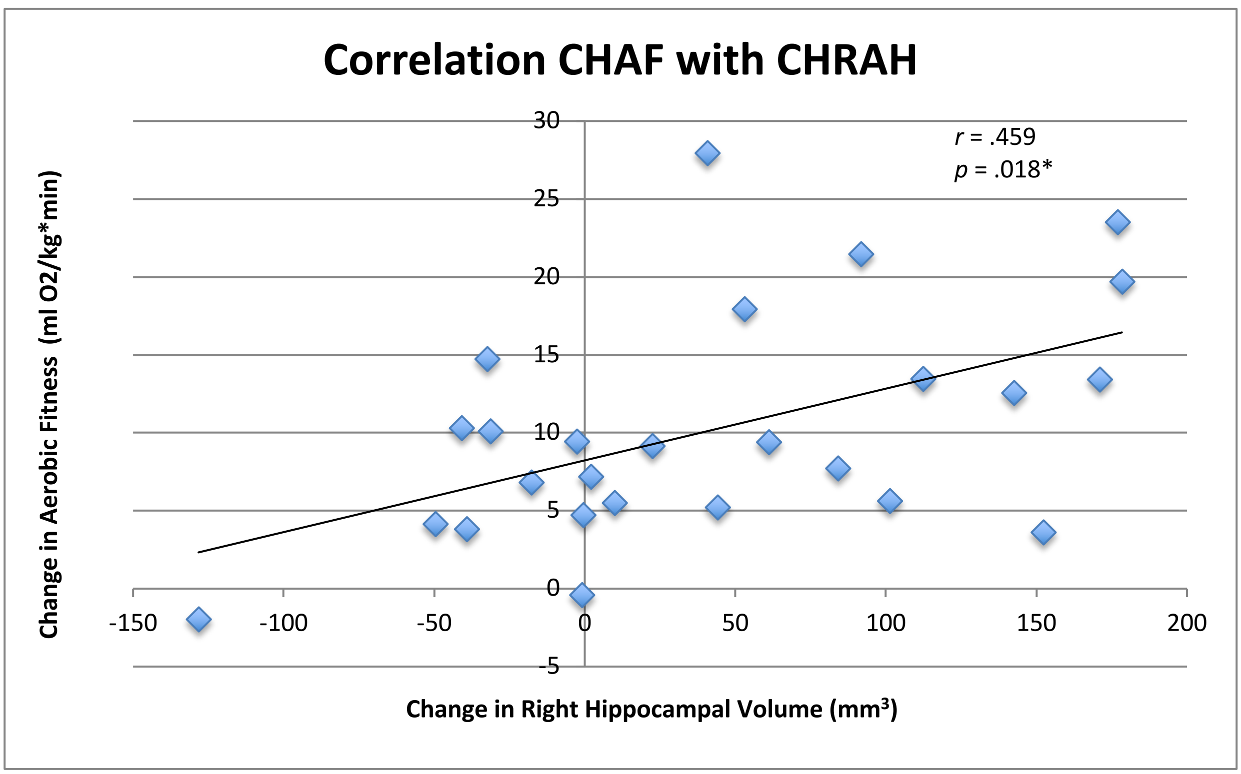

Figure 9. Correlation CHAF with CHRAH. CHAF; Change in Aerobic Fitness. CHRAH; Change in Right Anterior Hippocampal Volume. **p* < .05; ** *p* < .01; *** *p* < .001. *r* = Pearson's Correlation Coefficient.

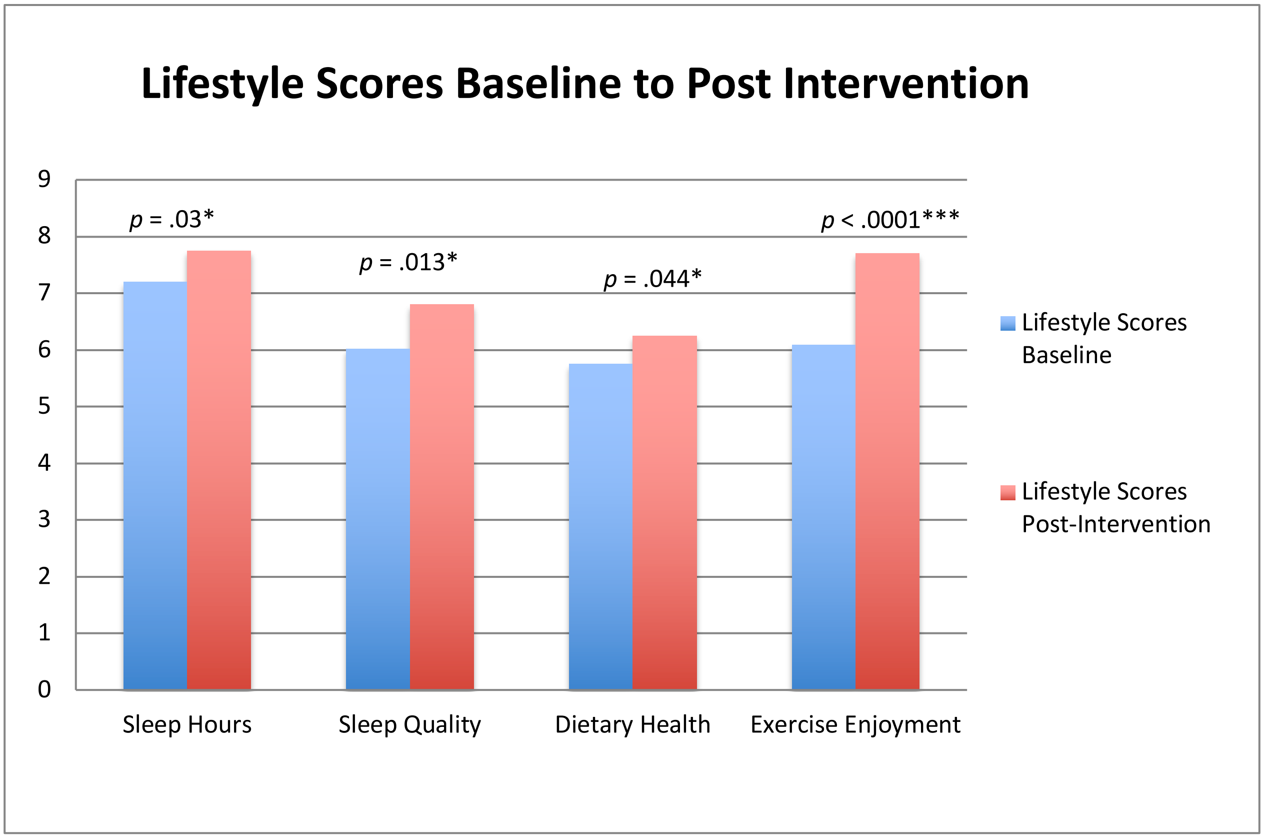

Figure 10. Lifestyle Scores at Baseline and Post Intervention. $^*p < .05$; $^{**}\ p < .01$; $^{***}\ p < .001$.

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