Effects of Obesity, Weight Loss, and Physical Activity on Brain Structure and Cognition

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Obesity in adults has been linked to altered brain gray matter volume and cognitive function. Weight loss may positively influence these aspects of brain health. However, evidence is inconsistent due to small sample sizes, short intervention lengths, and varying modes of treatment. Individual intervention components, such as physical activity, may influence gray matter volume and cognitive function differently. Data evaluating these relationships in the middle of the lifespan is lacking. **Purpose:** The purpose of this secondary analysis was to assess the associations between body weight, physical activity (PA), bilateral gray matter volume, and working memory in inactive adults with overweight or obesity participating in a 12-month behavioral weight loss intervention. **Methods:** Participants (N=115, Age=48 years [IQR: 42,52], BMI=32.4 kg/m^2 [IQR: 29.0, 35.4]) were randomized to DIET, DIET + MOD-PA, or DIET + HIGH-PA. All groups were prescribed a reduced-calorie diet (1200-1800 kcal/day) and behavioral intervention. DIET + MOD-PA and DIET + HIGH-PA groups were prescribed 150 min/week of moderate-to-vigorous PA (MVPA) and 250 min/week of MVPA, respectively. MET-min/wk of light-intensity PA (LPA) and MVPA were measured objectively. Working memory (reaction time (RT), accuracy (ACC)) was evaluated by the N-Back Task. Bilateral gray matter volumes (mm^3) of the hippocampus and basal ganglia were measured using 3T MRI and calculated using FSL segmentation algorithms. **Results:** At baseline, LPA was inversely associated with percent ACC difference (one-back subtracted from two-back) (β=-.003, p=.021), while MVPA was associated with absolute (β=$-3.26e^{-05}$, p=.016) and percent (β=-.003, p=.038) ACC difference. Higher volume

of MVPA was associated with bilateral nucleus accumbens volume (β=.044, p=008). Across the intervention, there were significant reductions in weight, one-back RT, two-back RT, with significant increases in volumes of LPA and MVPA. Weight loss was inversely associated with bilateral pallidum volume (β=-5.95, p=.046). Change in LPA was associated with changes in both absolute (β=-.027, p=.025) and percent (β=-.003, p=.043) RT difference and absolute (β=-5.51e^{-05}, p=.005) and percent (β=-.004, p=.026) ACC difference. **Conclusion:** Weight loss and PA may have a small influence on gray matter volume and working memory in middle-aged adults with overweight or obesity without other chronic health concerns.

Table of Contents

List of Tables

List of Figures

1.0 Introduction

1.1 Background

The obesity epidemic has continued on national and global levels. Within the United States, recent estimates suggest that the age-adjusted prevalence of obesity (Body Mass Index (BMI) ≥ 30 kg/m^2) among adults was 42.4% in 2017-2018.[1] These obesity rates have more than doubled over the past four decades and are accompanied by health and economic implications, raising a public health concern.[2]

The economic impact of obesity is demonstrated through elevated costs of medical care. Compared with adults of normal weight, adults with obesity are estimated to pay $2,505 more in medical care each year.[3] These expenditures for annual care have been shown to increase by class of obesity.[3] Similarly, obesity contributed to increases among all categories of direct medical costs including inpatient, outpatient, and prescription drug services. Overall, this led to an estimated total cost of $260.6 billion due to obesity in 2016.[3]

From a health perspective, individuals with obesity are placed at an increased risk of mortality, cardiovascular disease, metabolic syndrome, hypertension, type II diabetes, some forms of cancer, cerebrovascular disease, and other chronic conditions.[4-8] Obesity in mid-life has also been associated with an increased risk of dementia, however, this relationship does not hold in late-life.[9,10] Further links have been found between obesity and deficits in neurocognitive health including brain structure, function, and cognitive performance.[11]

At the structural level, as commonly measured by Magnetic Resonance Imaging (MRI), obesity has been consistently associated with reduced gray matter volumes in many cortical and

subcortical regions of the brain.[11-14] However, evidence demonstrating a relationship between obesity and both white matter volume and integrity has been mixed. Recently, technological advances (e.g., Diffusion Tensor Imaging (DTI) and MRI) have offered a pattern of findings suggesting that obesity is associated with poorer white matter volume and integrity.[15] Another component of brain structure shown to be affected by obesity includes the cerebrovascular architecture responsible for delivering oxygen, blood, and nutrients to the brain. Associations have shown reduced cerebral blood flow both globally and in prefrontal brain regions responsible for cognitive functions.[16,17]

Obesity has also been linked with dysfunctional brain activation compared to adults of a healthy weight.[18-20] This has been most commonly seen in both reward-stimulated and cognitive control-related regions of the brain, with literature supporting both hyper and hypoactivation of these areas. Specifically, as measured by Functional Magnetic Resonance Imaging (fMRI), individuals with obesity have shown increased activation in areas of the brain related to reward when presented with food cues.[18] However, decreased activation in areas of the brain related to executive function have been reported.[19] These measures of neurocognitive health are likely to negatively influence cognitive function in individuals with obesity.[11] An array of cognitive domains have been shown to be altered, especially executive function, learning, and memory.[11,21]

In addition to these changes in neural morphology and function, mechanisms that may contribute to the relationship between obesity and neurocognitive health are believed to involve increased inflammation, insulin resistance, vascular dysfunction, and other forms of metabolic dysfunction (e.g., decreased mitochondrial efficiency).[21-23] However, further research is warranted.

Given the financial and health burdens of obesity, there is a need for effective treatment strategies.[24] Treatment approaches involve dietary, physical activity, behavioral, pharmacological, and surgical methods, or a combination of such.[4] Of these, it has been stated that the most effective approach for weight loss and weight loss maintenance involve dietary, physical activity, and behavioral components.[4] This can be done through a standard behavioral weight loss intervention, with intentions to induce a meaningful weight loss of at least 5-10% of initial body weight in adults with obesity.[25] Weight loss of this magnitude has been associated with short and long-term benefits such as improvements in cardiometabolic health, physical function, quality of life, mood, sleep apnea, and more.[4,25-28]

The evidence in which weight loss impacts the structure, function, and physiology of the brain is overall inconsistent.[29] The literature also varies by method of weight loss, producing difficulty in teasing out the effects of each approach.[11,30] Structurally, findings suggest a lack of relationship, positive relationship, and negative relationship between brain structure and weight loss.[31,104-106] Much of the current literature, although limited, addresses the functional influence that weight loss may have. Specifically, decreased activation in response to food cues and increased activation in brain regions linked to cognition have been suggested.[20] In addition to these morphological findings, cerebral blood flow was seen to increase in frontal, parietal, and subcortical regions of the brain following a behavioral weight loss intervention.[32]

While brain function has been shown to change following weight loss,[18] the evidence regarding weight loss interventions and cognitive function remains unclear. Various domains of cognitive function have been shown to be positively associated with weight loss in adults with overweight or obesity.[30] Specific domains that have shown improvements include executive function, language, attention, and memory.[30] Further research is needed to assess the influence of

individual and combined weight loss methods on cognition, especially at the mechanistic level.[11,30] Mechanisms believed to contribute to the relationship between intentional weight loss and aspects of brain health include reduced insulin resistance/increased insulin sensitivity, reduced inflammation, and reduced oxidative stress.[30]

Individual intervention components involved in the treatment of obesity, such as physical activity, may influence aspects of overall and neurocognitive health independently. Examples of short-term benefits of physical activity include reduced feelings of short-term or state anxiety, reduced blood pressure, improved sleep, improved insulin sensitivity, improved aspects of some domain of cognitive functions, and more.[33] Some of these benefits are sustained due to regular physical activity. Long-term benefits include improved long-term or trait anxiety, sustained reductions in blood pressure, improved deep sleep, lower insulin levels, improved components of executive function, among others.[33] Physical activity has also been shown to offer risk reduction, delay, or prevention of some chronic conditions. These include a lower risk of all-cause mortality, cardiovascular disease and associated mortality, hypertension, type II diabetes, cancer (bladder, breast, colon, endometrium, esophagus, kidney, lung), and beyond.[33]

Additionally, research shows a reduced risk of developing cognitive impairment as physical activity has been shown to lower the risk of Alzheimer's disease and other dementias.[34,35] Physical activity interventions in adults with overweight or obesity have been shown to improve cardiorespiratory fitness (CRF), which was associated with components of hippocampal structure, an area of the brain heavily influenced by aforementioned conditions.[36] These findings supports a wealth of evidence presenting associations between physical activity and increased gray matter volume within the brain, particularly within the hippocampus and prefrontal cortex.[37,38] While the influence of physical activity on white matter has not been as readily studied, both interventional

and cross-sectional studies support the positive relationship between the two. Similarly, changes in white matter tracts between the aforementioned hippocampus and prefrontal cortex have been reported.[11]

In addition to these structural effects, physical activity has been related to changes in brain function as well. Alterations in functional connectivity within and between brain regions have been shown following physical activity interventions.[39,40] Moderately strong evidence suggests that physical activity improves domains of cognitive function such as executive function, processing speed, and memory.[33]

The pathways in which these structural and functional variations are seen are believed to involve increased neural plasticity. This plasticity is encouraging and provides hope for the treatment methods to reverse the negative neurocognitive effects of obesity. However, the mechanisms in which physical activity produces a change in brain health in humans are not fully understood.[41,42] Pathways may potentially include increased circulating levels of growth factors (e.g., Brain-Derived Neurotropic Factor (BDNF), Insulin-Like Growth Factor (IGF-1), Vascular Endothelial Growth Factor (VEGF)), decreased inflammation, decreased insulin sensitivity, improved aspects of metabolic function (e.g., mitochondrial biogenesis/efficiency), and psychosocial factors. Mechanisms are believed to occur on cellular/molecular, systemic, and behavioral levels. Separate levels of mechanisms are believed to converge and interact, but this remains to be investigated.[41,42] It is suggested that changes that occur on the cellular/molecular level may stimulate pathways at the macroscopic and behavioral levels, contributing to cognitive function.[42] These mechanisms may vary upon personal factors of the population in question (e.g., age), intervention parameters (e.g., mode), or brain region of interest (e.g., hippocampus).[41]

Overall, weight loss approaches, including physical activity, have shown to have a potential impact on the neurocognitive impairments related to obesity. A majority of the evidence in this area is cross-sectional in nature and does not appropriately target the causal pathways in which weight loss and physical activity interventions influence components of brain health.[29] Of the existing randomized controlled trials (RCTs), studies vary by design and method, further limiting the ability to draw conclusions on these mechanisms.[42] Therefore, rigorous RCTs are recommended to assess if and how weight loss and/or physical activity influence neurocognitive outcomes in adults with overweight and obesity.[11,30,41] It is important to assess the individual and combined contributions that weight loss and physical activity have on the brain in order to design interventions that are effective for promoting neurocognitive health in adults with obesity.[11,21]

While doing so, the limitations of current evidence from RCTs should be addressed. Regarding methods, the measurement of outcome and intervention components have varied.[42] While measuring obesity, many studies have utilized BMI. However, this technique is accompanied by limitations, including the inability to differentiate the distribution of adipose tissue. As this has shown to be a risk factor in neurocognitive impairment, more specific methods of body composition should be incorporated.[21] A detailed approach should be taken for the intervention as well. Despite the promising effect of physical activity on components of brain and cognitive health, it is possible that interventions varying by frequency, intensity, and type of movement may have alternate effects on these outcomes.[41] Currently, the prescription and dose of physical activity needed to maximize structural, functional, and physiological health of the brain is unknown.[11,33,43] In addition, many studies have not utilized statistical models that allow for better understanding of the pathways in which obesity, weight loss, and physical activity influence neurocognitive outcomes. Further research is needed to assess how these pathways may diverge

and converge.[42] Lastly, the current literature is saturated in two age ranges – children aged 6-13 years and adults aged 50 years and over. This contributes to gaps in the understanding of how weight loss or physical activity influence neurocognitive health across the lifespan.[33,43]

Thus, filling these needs was a focus of this study. A secondary data analysis of a completed RCT involving adults assists in addressing the spread within this age range. This analysis further informs the complex relationship between obesity, weight loss, physical activity, and aspects of brain health. Results can be used to inform how to properly design and adequately power RCTs to address these gaps in the literature. To do so, this study focused on the following aims and hypotheses.

1.2 Specific Aims

1. To examine the association between body weight and cognitive variables:
    a. To examine the association between baseline body weight and baseline cognitive variables prior to a 12-month behavioral weight loss intervention.
    b. To examine the association between change in body weight and change in cognitive variables during a 12-month behavioral weight loss intervention.
2. To examine the association between body weight and brain structure (specifically, subcortical structures such as the hippocampus and basal ganglia):
    a. To examine the association between baseline body weight and baseline brain structure (specifically, subcortical structures such as the hippocampus and basal ganglia) prior to a 12-month behavioral weight loss intervention.

b. To examine the association between change in body weight and change in brain structure (specifically, subcortical structures such as the hippocampus and basal ganglia) during a 12-month behavioral weight loss intervention.

3. To examine the association between physical activity (including subcomponents of MVPA and LPA) and cognitive variables, controlling for body weight:
    a. To examine the association between baseline physical activity levels (including subcomponents of MVPA and LPA) and baseline cognitive variables, controlling for body weight, prior to a 12-month behavioral weight loss intervention.
    b. To examine the association between change in physical activity levels (including subcomponents of MVPA and LPA) and change in cognitive variables, controlling for body weight, during a 12-month behavioral weight loss intervention.
4. To examine the association between physical activity (including subcomponents of MVPA and LPA) and brain structure, controlling for body weight:
    a. To examine the association between baseline physical activity levels (including subcomponents of MVPA and LPA) and baseline brain structure (specifically, subcortical structures such as the hippocampus and basal ganglia), controlling for body weight, prior to a 12-month behavioral weight loss intervention.
    b. To examine the association between change in physical activity levels (including subcomponents of MVPA and LPA) and change in brain structure (specifically, subcortical structures such as the hippocampus and basal ganglia), controlling for body weight, during a 12-month behavioral weight loss intervention.

5. Exploratory Aim: To examine the associations between cognition and brain structure:
    a. To examine the association between baseline cognitive and brain structure volumetric variables, prior to a 12-month behavioral weight loss intervention.
    b. To examine the association between cognitive and brain structure volumetric variables, following a 12-month behavioral weight loss intervention.

1.3 Hypotheses

1. It was hypothesized that:
    a. There would be an inverse association between baseline body weight and baseline cognitive variables, where a higher baseline body weight would be related to less favorable levels of baseline cognitive variables.
    b. There would be an inverse association between change in body weight and change in cognitive variables, where the magnitude of reduced body weight would be related to the magnitude of more favorable levels of cognitive variables.
2. It was hypothesized that:
    a. There would be an inverse association between baseline body weight and baseline brain structure where a higher baseline body weight would be related to smaller baseline brain structure.
    b. There would be an inverse association between change in body weight and change in brain structure, where the magnitude of reduced body weight would be related to the magnitude of increased size of brain structures.

3. It was hypothesized that:
    a. There would be a negative association between baseline physical activity levels and baseline cognitive variables, where lower baseline physical activity levels would be related to less favorable levels of baseline cognitive variables.
    b. There would be a positive association between change in physical activity levels and change in cognitive variables, where the magnitude of increase in physical activity would be related to the magnitude of increase in levels of cognitive variables.
4. It was hypothesized that:
    a. There would be a negative association between physical activity levels and baseline brain structure, where lower baseline physical activity levels would be related to smaller baseline brain structure.
    b. There would be a positive association between change in physical activity levels and change in brain structure, where the magnitude of increase in physical activity would be related to the magnitude in increased size of brain structures.
5. Exploratory Aim: It was hypothesized that:
    a. There would be an association between cognitive and brain structure variables, including both basal ganglia and hippocampal regions of the brain.
    b. There would be an association between cognitive and brain structure variables, including both basal ganglia and hippocampal regions of the brain.

1.4 Future Implications

By addressing the aforementioned aims and hypotheses, this secondary analysis further elucidates the links between obesity, weight loss, physical activity, and the brain. In doing so, this project allows us to understand if these neurocognitive variables may be intervention targets in adults with obesity. This is especially important to understand within middle-aged adults, an area of the lifespan that is not as readily studied in current neurocognition literature, to fully understand how comorbidities and lifestyle behaviors contribute to brain health. Additionally, this analysis may help to inform and improve translational approaches to obesity management in health care. Thus, the following sections of this document will highlight key areas of consideration while informing the current and potential work in this space.

2.0 Review of the Literature

2.1 Obesity

2.1.1 Definition of Obesity

Obesity guidelines categorize obesity in adults by BMI.[4,25] BMI is calculated by dividing weight in kilograms by squared height in meters. A BMI of greater than or equal to 25.0 to < 30.0 kg/m^2 is considered overweight, while a BMI of greater than or equal to 30.0 kg/m^2 is considered obese. Obesity can be further classified by subdivisions of BMI. Class I obesity ranges from a BMI of 30.0 to < 35.0 kg/m^2, Class II from 35.0 to < 40.0 kg/m^2, and Class III from ≥ 40.00 kg/m^2. Class III obesity has also been referred to as 'severe obesity'.

2.1.2 Prevalence of Obesity

According to the most recent data from the National Health and Nutrition Examination Survey (NHANES) reflecting 2017-2018, the age-adjusted prevalence of obesity of adults in the United States was 42.4%. The differences in the prevalence of obesity by age group and by sex were not statistically significant. By race, overall, the prevalence of obesity was lowest in non-Hispanic Asian adults and the highest in non-Hispanic black adults with a prevalence of 17.4% and 49.6% respectively.[1]

Compared to the most recently reported age-adjusted prevalence of 42.4%, obesity rates have more than doubled over the past four decades.[2] According to the NHANES survey period

from 1976-1980, the prevalence of obesity among adults aged 20-74 was 15.0%.[2] The following rapid increase in the prevalence of obesity marked the epidemic that continues today.[44] These increasing obesity rates are accompanied by health and economic implications, raising a public health concern.

2.1.3 Consequences of Obesity

Obesity is a multi-faceted chronic disease that contributes to health and economic implications. Given the intricate nature of obesity, the etiology of this disease has yet to be fully understood. In general, excess body weight contributes to an elevated BMI, used in part to identify obesity. Excess body weight is believed to be a result of an energy imbalance. As shown in Figure 1, energy balance is achieved when energy intake is equal to energy expenditure. While in energy balance, it is believed that weight is stable. However, a negative or positive energy imbalance is theorized to result in a loss or gain of body weight, respectively. In the context of obesity, a positive energy imbalance may result from increased energy intake, decreased energy expenditure, or both. As a further example, an increase in energy intake through the consumption of excess calories will upset the equilibrium within energy balance and result in a positive energy balance.

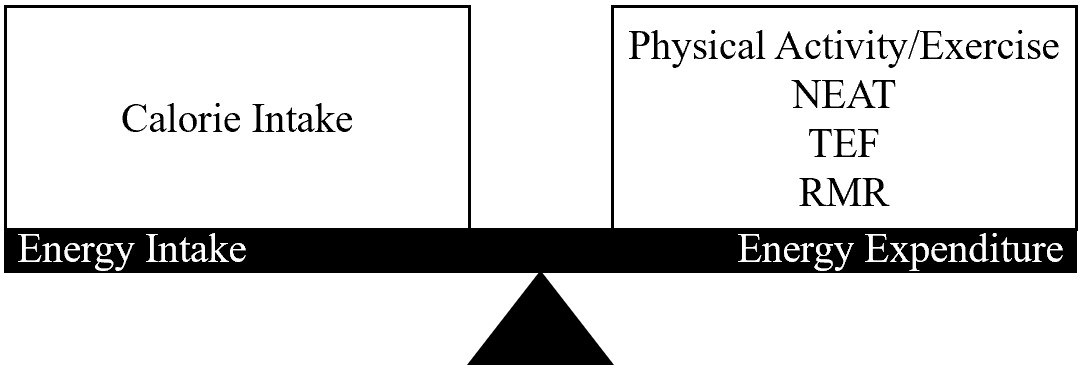

Figure 1 Diagram of Energy Balance Equation

However, within this seemingly simple formula, energy intake and energy expenditure may interact. For example, an increase in physical activity (energy expenditure) may impact calorie intake (energy intake), contributing to variability in weight change. Beyond the energy balance variables, there are potential factors that may interact with either side of the energy balance equation.[44] Contributing elements to the complexity of this condition include genetic, environmental, biological, social, and other factors.

Obesity has been associated with increased morbidity and mortality.[25,45] The literature has consistently reported a positive association between increasing BMI and risk of all-cause and cardiovascular disease mortality.[5-8,25] Through similar patterns, obesity contributes to an increased risk of morbidity from CVD (fatal and nonfatal), coronary heart disease (CHD) (fatal and nonfatal), stroke (overall, ischemic, and hemorrhagic), metabolic syndrome, type II diabetes, some forms of cancer, hypertension, dyslipidemia, gallbladder disease, sleep apnea, osteoarthritis, and respiratory problems.[4,25]

In addition to these health conditions, obesity negatively impacts functional capacity including physical function and health-related quality of life (HRQOL).[46,47] The implications of

obesity on neurocognition can be found in Section 2.5 within this document. Thus, the negative effects of overweight and obesity demonstrate the need for strategies that prevent, minimize, or treat excessive weight gain.[25]

2.2 Health Benefits of Weight Loss

Modest reductions in body weight have been linked to improvements in health consequences of overweight and obesity.[4] Weight loss interventions have been shown to contribute to a reduction in all-cause and disease-specific mortality rates.[48] Risks for developing chronic diseases are also reduced with certain amounts of weight loss.[25] For example, in at-risk individuals including adults with overweight or obesity, intentional weight loss contributes to a reduced risk of developing type II diabetes. With an average follow-up of 2.8 years, participants in the lifestyle intervention of the Diabetes Prevention Program (DPP) had a mean significant weight loss of 5.6 kg, contributing to a 58% relative reduction in the risk of developing type II diabetes.[25,49] A weight loss of at least 5-10% of initial body weight may contribute to reduced blood pressure, reduced total and low-density lipoprotein (LDL) cholesterol, increased high-density lipoprotein (HDL cholesterol), reduced triglycerides, reduced hemoglobin A_{1C} (HbA_{1C}), among other improvements including a reduced need for medications to regulate some of the aforementioned risk factors.[25] Data from the Look AHEAD trial, involving individuals with overweight or obesity and type II diabetes, support the influence of weight loss on these claims.[50,51] Following one year of an intensive lifestyle intervention, a mean weight loss of 8.6% was found among participants. Those who reduced their body weight by 5 to <10% were at significantly increased odds of achieving reduced systolic and diastolic blood pressures (5 mmHG), increased HDL cholesterol (5 mg/dL),

reduced triglycerides (40 mg/dL), and reduced HbA_{1C} (0.5% points).[50,51] Further, greater weight loss was associated with greater clinically meaningful improvements in these risk factors.[50]

In addition to the aforementioned benefits of weight loss on morbidity and mortality in adults with obesity, a reduction in body weight has also been shown to improve physical function and HRQOL in this population.[46,52] Weight loss may also be important for neurocognitive health. This information has been outlined in Section 2.6 within this document.

2.3 Treatment of Obesity

Given the vast and far-reaching impact of obesity, there is a need for interventions that are affective for producing weight loss.[24] In order to do so, there are a variety of treatment approaches that include the use of single or multiple dietary, physical activity, behavioral pharmacological, or surgical intervention approaches. However, of these, it is recommended that an approach involving dietary, physical activity, and behavioral components is the most effective for weight loss and weight loss maintenance.[4,25,53]

2.3.1 Methods of Weight Loss: Behavioral Weight Loss Interventions

2.3.1.1 Dietary Component

During dietary modification, individuals should take in less energy than they expend in order to produce an energy deficit. Prescription of a moderately-reduced diet includes a deficit of 500-1000 kilocalories (kcal) per day.[4,25] These recommendations have been assigned by sex or baseline weight at the start of an intervention and typically range from a prescription of 1200-1800

kcal/day.[25] This prescription prepares participants for a weight loss goal of 0.5-1 kg loss per week.[4,54] Diets of varying macronutrient composition can be affective if they contribute an appropriate energy deficit.[25,55,56] Specifically, it is typically recommended to consume a high-carbohydrate and low-fat diet while facilitating the caloric deficit of 500-1000 kcal per day.[56] Other recommendations include very low-calorie diets (VLCD), meal replacements, portion-control, and other strategies, some of which can result in more weight loss than a conventional energy restricted diet.[56]

2.3.1.2 Physical Activity Component

Physical activity increases total energy expenditure, contributing to the negative energy balance needed for weight loss. Physical activity has been employed as a main approach to weight loss, however, multiple studies have shown that this modality alone does not exceed a loss of 3 kg, or 1-3% of body weight.[57,58] It has been shown that physical activity has independent benefits to health, however, a volume threshold must be reached in order to assist with weight loss. Specifically, physical activity performed for less than 150 minutes/week results in minimal weight loss, physical activity greater than 150 minutes/week results in modest weight loss of approximately 2 to 3 kg, and physical activity of 225 to 420 minutes/week contributes up to 5 to 7.5 kg of weight loss.[57] Therefore, there is evidence for a dose-response relationship between amount of physical activity and the magnitude of weight loss.[58] Approaches typically include activity in the form of aerobic exercise of at least 150 min/week, with a goal of maintaining 200-300 min/week.[25,59] Strategies to achieve these recommended activity levels include performing physical activity in short bouts, accumulating steps, conducting interventions in either supervised or unsupervised settings, and others.[34,58,60-62]

2.3.1.3 Behavioral Component

In order to receive the benefits offered by these behaviors, we need individuals to not only perform them, but adopt them into their lifestyle. The goal of behavioral treatment is for individuals to adhere to the reduced caloric intake and increased physical activity prescriptions, and to incorporate these changes into their lifestyle. To do so, the use of behavioral theories and constructs such as the Transtheoretical Model, Social Cognitive Theory, Self-Determination Theory, Theory of Planned Behavior, and others have been recommended.[63-67] This is done through a structured behavior change program involving the self-monitoring of diet, physical activity, and body weight. Additional strategies include progression, feedback, goal setting, enhancing self-efficacy, barrier identification, stimulus control, social support, relapse prevention, problem solving, and others.[54-56,68-70] The timing of this content has been proven to be influential on weight loss success. It is recommended that sessions be held at a minimum of once a month, with further success shown at a frequency of bi-weekly or weekly visits. Sessions may range from 60 to 90 minutes, and are led by trained professionals.[54] Sessions are usually held for 16-26 weeks followed by less frequent sessions once progressing from short into long-term interventions.[54]

2.3.2 Short-Term Weight Loss Strategies and Results

Although these components offer benefits independently, diet, physical activity, and behavior modification are employed together for the best outcomes in both short and long-term interventions. Short-term (less than or equal to 6 months in duration) involve the diet and physical activity prescriptions mentioned previously, with a progressive transition to achieve these results. While doing so, behavioral sessions during this period are held for 16-26 weeks.[54] This approach has resulted in the loss of 5-10% of initial body weight, contributing to associated health benefits. An average weight loss of 8 kg in 6 months has been seen.[25]

Weight loss within the first month of treatment is predictive of long-term weight loss. It has been shown that individuals who have lower weight loss within the first month are less likely to be successful long-term.[71] There is a clear relationship between short and long-term success, and treatment components that are employed may be similar or vary as time progresses.

2.3.3 Long-Term Weight Loss Strategies and Results

Long-term interventions are considered greater than or equal to 12 months in duration. Of the 3 intervention components described previously, physical activity may play a key role in long-term weight loss and the prevention of weight regain. While it was previously mentioned that physical activity alone is of limited benefit for inducing weight loss, is important for facilitating long-term weight management.[55] Studies have repeatedly shown that over 250 minutes of physical activity per week is needed for weight loss maintenance, as greater levels of physical activity are associated with lower levels of weight regain.[57]

In the treatment of obesity, the maintenance of weight loss continues to pose a challenge. Behavioral weight management programs have been successful in producing weight losses of 8-10% of initial body weight, yet many participants go on to regain almost half of this lost weight within a year, and return to baseline weight within 5 years.[54,72] It is believed that this is due to a complex interaction between behavioral, physiological, and other mechanisms.[69]

To prevent weight regain, another effective method may be continued behavioral support on an every-other-week or monthly basis. Wing and colleagues demonstrated this to be true through the use of monthly weight loss maintenance sessions that contributed to attenuated weight regain for 18 months. A target of these sessions was on daily self-weighing, a skill specific to the maintenance of weight loss, which showed to be associated with successful weight loss maintenance.[73,74] Additional strategies can be learned from The National Weight Control Registry. Examples include the consumption of low-fat diets, maintain dietary consistency, high levels of regular physical activity, among others.[75]

2.4 Benefits of Physical Activity

Individual intervention components involved in the treatment of obesity, such as physical activity, may influence aspects of overall and neurocognitive health independently. Research demonstrates that participating in regular MVPA provides many health benefits while preventing potential adverse health outcomes.[53] Strong evidence supports an inverse dose-response relationship between MVPA and all-cause mortality and cardiovascular disease mortality.

In addition, strong evidence supports the positive influence of physical activity on morbidity. Specifically, an inverse relationship exists between greater amounts of MVPA and reduced risk of CVD, CHD, ischemic stroke, heart failure, hypertension, type II diabetes, some forms of cancer, obesity, osteoporosis, and others.[33]

Beyond the contributions to mortality and morbidity, further results may be seen immediately following a bout of physical activity while others are produced over time. These include reduced blood pressure, improved insulin sensitivity, improved physical function, and more.[33] By performing 150-300 minutes of MVPA per week, physical activity has also been shown to offer risk reduction, delay, or prevention of some chronic conditions, and improvement in risk factors. Sustained benefits of regular physical activity include sustained reductions in blood pressure, lower insulin levels, improvements in aspects of physical fitness (such as improved cardiorespiratory fitness, improved muscular strength), among others.[33] These benefits have been shown to outweigh most risks or concerns of physical activity including adverse events (such as a myocardial infarction) or injury.[53] Further benefits can be received by performing additional MVPA beyond the 300 minute/week threshold.

The following sections address aspects of neurocognition as it relates to obesity, weight loss, and lifestyle factors that influence brain health. Section 2.7 addresses the relationship between physical activity and neurocognition.

2.5 Neurocognition and Obesity

As outlined in Section 2.1.3, obesity negatively influences aspects of health including mortality, morbidity, and risk factors of such. Despite the related comorbidities, obesity appears

to be an independent risk factor for dementia. In an epidemiological study involving 10,276 middle-aged men and women, compared to individuals of a normal weight, individuals with obesity were at a 74% increased risk of dementia.[76] Other studies have repeatedly shown a relationship between obesity and increased risk of dementia in mid-life, and has held in consideration of specific types of dementia as well.[9,77] Whitmer and colleagues demonstrated that adults with obesity in midlife were at 3.10 and 5.01 times higher risk of Alzheimer's disease and vascular dementia respectively in comparison to those of a normal BMI.[77] However, while obesity in mid-life is predictive of dementia, this relationship does not hold in late-life. Fitzpatrick and colleagues found that obesity in mid-life increased the risk of dementia compared to individuals of a normal BMI, while obesity in late-life decreased the risk of dementia.[78] This inverse relationship is characteristic of the "obesity paradox". This phenomenon suggests that obesity in late-life may be protective. In addition to evidence supporting the obesity paradox, neuroimaging has allowed for the identification of mid-life as a critical period of brain development.[79] However, beyond this paradox, obesity has shown to effect brain health in older adults beyond those seen as a result of normal aging. While this relationship is not yet fully understood, it may be that obesity accelerates the development and onset of neurocognitive impairments seen in late life.[11]

In addition, obesity has been associated with components of brain health including mood disorders, anxiety disorders, depression, poor sleep, among others.[80,81] Obesity has also been related to altered structure and function of the brain, independent from related comorbidities.[20,21] Technological advances in neuroimaging have promoted a better understanding of these relationships, and allowed for the further evaluation of linkages between obesity, neurocognition, and lifestyle behaviors.[20]

2.5.1 Brain Structure and Obesity

From a structural perspective, the gray matter, white matter, and cerebrovasculature of the brain have been shown to be related to obesity and increased BMI.[10] Changes in global and regional gray matter within the brain have been consistently linked to obesity and elevated BMI.[10] One of the most readily studied areas of the brain includes the hippocampus, which has consistently shown to be negatively linked to obesity.[12,82] The hippocampus is an important brain structure within the medial temporal lobe involved in episodic and relational memory formation. This critical region is unfortunately susceptible to damage from neurodegeneration, which may occur earlier and faster compared to other areas of the brain.[11,83] In a study by Raji and colleagues, individuals with obesity had reduced gray matter volume in regions such as the hippocampus, prefrontal cortex, the basal ganglia, and other subcortical regions compared to individuals of a healthy weight. These relationships held after controlling for comorbid conditions, suggesting the influence of obesity on brain atrophy.[12]

This study by Raji and colleagues highlights another important region of the brain suggested to be influenced by obesity - the basal ganglia.[12] The basal ganglia are a group of subcortical core and associated structures. Within the telencephalon are the core components including the global pallidus and the striatum (caudate and putamen). The associated components of the basal ganglia include the subthalamic nucleus (located in the diencephalon), the substantia nigra (located in the mesencephalon) and the pedunculopontine nucleus (located in the pons).[84,85] These nuclei work to control movement, behavior, emotions, attention control, and other functions. Similar to the hippocampus, the basal ganglia have been shown to atrophy in late life, preceding age-related cognitive decline.[86]

The exclusive influence of obesity alone on gray matter volume was also suggested by Medic and colleagues.[14] In a study of 203 self-reported healthy adults with no known comorbidities, BMI was associated with cortical thinning in the ventromedial prefrontal cortex and lateral occipital cortex.[14] In addition to these studies, other brain regions that may be affected include the orbitofrontal cortex, hypothalamus, cerebellum, brain stem, and beyond. These areas of the brain are linked to brain functions such as decision making, satiety, motivation, reward, and other brain functions that are linked to behaviors that contribute to obesity.

Studies have found negative, positive, and lack of relationship between obesity and white matter volume, contributing to mixed findings.[12,87-89] Through the use of Diffusion Tensor Imaging and Fractional Anisotropy, studies have shown that the structural integrity of white matter tracts are generally reduced in consideration of obesity. Specifically, obesity-related decreases in fractional anisotropy have been observed in white matter tracts connecting the frontal and temporal lobes, and the limbic region.[15,89,90] In addition, white matter hyperintensities, as revealed through structural MRI, have been positively associated with BMI, suggesting demyelination throughout the brain.[91,92] These technological advances have revealed associations between obesity and reduced health and integrity of white matter within the brain.

In addition to the aforementioned morphological relationships, links have also been found between obesity and reduced cerebral blood flow within the brain. This has been shown both globally and regionally within the brain. For example, using single photon emission computed tomography (SPECT) imaging, Willeumier and colleagues found that a higher BMI was associated with reduced cerebral blood flow in the prefrontal cortex, an area of the brain involved in attention, reasoning, and executive function.[17]

2.5.2 Brain Function and Obesity

Obesity-related abnormalities in brain function have been identified in a variety of regions within the brain.[11] Functional neuroimaging modalities have allowed for the dissection of the complex relationship between functional brain activity and obesity.[20] Pursey and colleagues conducted a systematic review of 60 studies involving obesity and fMRI.[18] Of these, adults with obesity consistently demonstrated increased activation in areas of the brain related to reward, such as limbic and orbitofrontal regions, when presented with visual food cues.[18] Outside of this context, a study by Gonzales and colleagues used fMRI techniques to assess functional activation while performing a cognitive task (two-back working memory task).[19] Compared to the groups with normal and overweight BMIs, the group with obese BMIs demonstrated both a poorer performance on the two-back working memory task and a lower activation in the right parietal cortex.[19] Overall, when compared to adults of a healthy weight, obesity is associated with altered functional activation within the brain, particularly in reward, cognitive control (learning, memory formation and recall, and self-referential cognitive processes), and feeding behavior-related (disinhibition) regions.

2.5.3 Cognitive Function and Obesity

Therefore, in addition to dysregulated brain function, cognitive function has shown to be negatively influenced by obesity. Overall, obesity has been negatively associated with a variety of domains of cognitive function. This has been demonstrated cross-sectionally as higher BMI has been associated with lower cognitive performance after controlling for age, sex, level of education, level of physical activity, and region of residence.[93] In this same study, longitudinal associations

showed a relationship between a higher BMI at baseline and greater decline in cognition after five years.[93] In a review article by Smith and colleagues, 14 of the 15 cross-sectional studies involving adults 19-65 years of age consistently showed that obesity and cognition were negatively associated.[94] Further, of the 14 cross-sectional studies demonstrating this relationship, 11 revealed poorer executive function.[94] To complement these findings, associations suggest that obesity and related comorbid conditions may serve as risk factors for components of impaired cognition.[79] However, believed to be in-part due to the potential confounding of these comorbidities, this evidence has been inconstant.[79]

2.5.4 Factors and Mechanisms of Neurocognition and Obesity

Obesity and associated chronic conditions may contribute to the pathophysiological mechanisms influencing brain health through peripheral pathways. In order to understand the influence of chronic conditions on aspects of brain health, these peripheral processes assist in understanding potential mechanisms.[11] Pathways are believed to include inflammation, blood pressure (vascular dysfunction), insulin resistance, altered morphology within the brain, and others.[11,95] For example, obesity is categorized by excess body weight, but also excess adipose tissue. This adipose tissue is metabolically active as it secretes metabolic, hormonal, and inflammatory products such as C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor α and other signals. These inflammatory markers, specifically CRP and IL-6, have been associated with cognitive decline and low cognitive performance.[96,97] Inflammatory pathways involving adipokines are believed to contribute to arterial stiffness and hypertension, which may both contribute to alterations in cerebral circulation.[22]

Excess adipose tissue also has vascular consequences. Associations between obesity and activations of the renin-angiotensin-aldosterone system contribute to increased sodium reabsorption in the kidneys, and increased procoagulants. Together, these mechanisms present through increased cardiac output, endothelial dysfunction, and stiffening of arteries that contribute to increased blood volume.[98] This vascular damage may contribute to deficits in cognitive function.[99]

Obesity also contributes to both central and peripheral insulin resistance, which contribute to elevated glucose levels and elevated blood pressure through altered kidney function in the form of renal sodium retention.[98] Aside from the neurological consequences of vascular damage previously described, peripheral insulin resistance may influence central insulin resistance. This may be through reduced cognitive function believed to be related to reduced central insulin sensitivity.[100,101] Further, a study by Cheke and colleagues (2017) demonstrated that the magnitude of insulin resistance was negatively related to memory.[102]

Overall, the information provided to support these claims are largely cross-sectional, and do not appropriately target mechanisms.[29]. Despite these limitations, there is a need for effective treatments of obesity. By investigating the mechanisms involved, research will appropriately direct efforts to develop effective pharmacological and non-pharmacological treatments of obesity.

2.6 Neurocognition and Weight Loss

Weight loss has been associated with improvements in brain-health related outcomes such quality of life, mood, sleep, etc.[103] However, the literature presenting the influence of weight loss on aspects of brain health including the structure, function, and cognitive function of the brain is quite limited and inconsistent.

2.6.1 Brain Structure and Weight Loss

Inconsistent findings have been presented between brain structure and weight loss, suggesting a lack of relationship, positive relationship, or negative relationship. A study by Drummen and colleagues observed individuals participating in an 8-week dietary weight loss intervention followed by a 22-month weight maintenance period.[104] During both the intervention and maintenance periods, there were no significant changes in global gray matter volume. There was also no relationship observed between gray matter volume with weight loss or long-term weight maintenance.[104] However, a randomized controlled trial by Prehn and colleagues presented more encouraging results.[105] Following a 12-week dietary intervention, the group of older adults that underwent caloric restriction presented with increased gray matter volume in the hippocampus, in addition to the inferior frontal gyrus within the brain. Meanwhile, gray matter volume reductions were simultaneously seen in the olfactory cortex, postcentral gyrus, and cerebellum/vermis.[105] A negative relationship was also suggested by a study involving a 3-month dietary weight loss intervention where successful dieters showed a greater reduction in gray matter volume in the left precentral gyrus and insula.[106] The literature describing the influence of weight loss on the basal ganglia is scarce.

Following a 6-week very low-calorie dietary intervention, global and regional gray matter volumes were unchanged. However, results showed a decrease in both global and regional white matter volume within the left temporal lobe.[106] White matter was also studied in a subsample of the Look AHEAD trial, 10-12 years after enrollment. In the Look AHEAD study, participating adults with overweight or obesity and type II diabetes were randomized to receive either a lifestyle intervention (diet, physical activity, and behavioral intervention components) or diabetes support and education. Compared with participants in the diabetes support and education group, participants who received the lifestyle intervention associations showed mean reductions in white matter hyperintensity and mean ventricle volumes of 28% and 9%, respectively.[31]

2.6.2 Brain Function and Weight Loss

Similarly, evidence contributing to relationships between brain function and weight loss has been inconsistent. In studies employing dietary restriction as the method of weight loss, decreased activation in response to food cues was found in brain regions linked to reward processing. This has been seen in interventions lasting as little as 4 weeks.[107] In addition, increases in activation to brain regions linked to cognition were also found following this acute dietary intervention.[11,107] Despite being a different weight loss approach, results were found in studies utilizing bariatric surgery, where individuals showed a decrease in functional activation in areas related to reward processing, with less of a response to visual food cues [21].

2.6.3 Cognitive Function and Weight Loss

The relationship between cognitive function and weight loss remains unclear. A meta-analysis by Siervo and colleagues, involving diet and bariatric surgery interventions, demonstrated an association with weight loss and low-order improvements in cognitive performance in attention and executive control.[108] However, this relationship only held for individuals with obesity as opposed to individuals who were overweight.[108] Similar findings were shown in a meta-analysis by Veronese and colleagues, including randomized controlled trails and longitudinal studies where weight loss was induced by diet, physical activity, and surgical approaches. Findings showed an association between weight loss and improvements in attention, memory, executive function and language.[30]

A subsample of individuals participating in the Longitudinal Assessment of Bariatric Surgery project aged 20-70 years completed cognitive assessments prior to bariatric surgery and 12-weeks, 12-months, 24-months, and 36-months following surgery.[109-111] Prior to undergoing bariatric surgery, patients had clinically meaningful impairments of some domains of cognitive function. Of the bariatric surgery patients, 12.0% demonstrated impairments in memory, 8.0% demonstrated impairments in executive function, 4.0% demonstrated impairments in attention, and 4.0% in language. Following surgery, there was a significant main effect across the five timepoints for attention, executive function, and amemory.[109] Therefore, these results demonstrates that certain domains of cognition can be improved and maintained following surgical weight loss interventions.

2.6.4 Factors and Mechanisms of Neurocognition and Weight Loss

As outlined in Section 2.2, weight loss improves the morbidity and risk factors that present with obesity. Overall, it is believed that intentional weight loss may influence neurocognitive health through the morphological and functional changes previously described, in addition to reduced insulin resistance/increased insulin sensitivity, reduced inflammation, and reduced oxidative stress.[30] However, mechanisms in which weight loss may impact aspects of brain health may vary by method.

Specific to dietary changes, caloric restriction has been shown to increase the number and efficiency in the mitochondria, reduce oxidative stress, and enhance neurogenesis.[42] These bioenergetic responses are related to the brain through neurotrophic factors within the brain. For example, BDNF has shown to stimulate the biogenesis of mitochondria and promote neuronal resistance to forms of stress.[112,113]

A mechanism specific to bariatric surgery may be the influence on neurohormones related to appetite. For example, leptin and ghrelin are neurohormones driving appetite that have been shown to be dysregulated in obesity. However, decreased leptin levels and increased ghrelin levels seen post-bariatric surgery have been shown to predict improvements in cognitive functions, specifically attention and executive function, one year after surgery.[114,115] In addition, metabolic changes such as reduced insulin resistance and improved glycemic control have been shown to predict improvements in cognition following surgical interventions.[116] Similarly, improved glycemic control has been related to better cognition post-surgery including improved aspects of attention and executive function.[117]

Further research is needed to identify if the effects of different methods of weight loss on brain health and cognitive health are independent or overlapping, and if they are influenced by

comorbidities of obesity.[11,41] Overall, weight loss approaches, including physical activity, have shown to have a potential impact on the neurocognitive impairments related to obesity.[11]

2.7 Neurocognition and Physical Activity

Physical activity is a component of weight loss approaches. Strong evidence shows an association between higher volumes of physical activity and a reduced risk of cognitive decline and dementia, including Alzheimer's disease. Specifically, physical activity has been shown to contribute to a 35 – 39% reduced risk of developing cognitive decline.[33-35] Sofi and colleagues found a 38% reduced risk of cognitive decline in individuals reporting the performance of high levels of exercise compared to sedentary individuals. Even low-to-moderate levels of activity contributed to a 35% reduced risk of cognitive decline.[34] Beckett and colleagues demonstrated a 39% reduced risk of developing Alzheimer's disease in older adults who were physically active compared to non-active comparators.[35]

As mentioned in Section 2.4, there are both short and long-term benefits that present following physical activity. Specific to brain health, short-term benefits of physical activity include reduced feelings of short-term or state anxiety, improved sleep, improved aspects of some domain of cognitive functions, and more.[33] Long-term benefits to brain health include improved long-term or trait anxiety, improved deep sleep, improved components of executive function, among others.[33] In addition, physical activity has been shown to positively influence other aspects of health including the structure, function, and cognitive function of the brain.

2.7.1 Brain Structure and Physical Activity

Higher levels of physical activity have shown to be associated with larger gray matter volumes within the brain.[118,119] It has been proposed that physical activity may not influence all areas of the brain the same, suggesting a regionally specific relationship.[120,121] This has been seen through increased volume within the hippocampus, prefrontal cortex, areas of the basal ganglia, and other regions.[122] Of these, the prefrontal cortex and hippocampus have been the most readily studied. Despite these associations, other cross-sectional studies have found that these relationships may be dependent upon factors such as age, BMI, and stress levels,[87,123,124] while others found a lack of association.[125]

Given the possible confounders or potentially negligible relationship not captured by cross-sectional analyses, randomized controlled trials and longitudinal studies have shed more light on these relationships.[37,38,126,127] A longitudinal study conducted by Erickson and colleagues demonstrated that higher amounts of baseline physical activity, in the form of walking, were associated with greater gray matter volumes in the frontal, temporal, and occipital regions of the brain after a 9-year follow-up. Later, greater volume of gray matter in the hippocampus and other brain areas, specifically in the inferior frontal gyrus and supplementary motor area, were associated with lower risk of cognitive impairment.[127] Similar results were shown in a study by Colcombe and colleagues following a 6-month intervention, where the group performing aerobic exercise demonstrated an increase in gray matter volume in areas such as the prefrontal cortex, anterior cingulate cortex, and lateral temporal lobes. However, the control group performing stretching and toning movements saw a slightly reduced gray matter volume in the same areas of the brain.[38] Erickson and colleagues also employed an aerobic exercise intervention for 1 year, where 120 older adults were randomized to an aerobic exercise group or stretching control group. Following

the intervention, the aerobic exercise group demonstrated a significant 2% increase in hippocampal volume, while the stretching control group experienced a 1.4% decline.[37] The authors mentioned that the results in the stretching control group are consistent with the natural shrinkage in hippocampal volume annually in this population. Overall, these results demonstrate that an exercise regimen adopted later in life can influence the size of the hippocampus. As this brain structure can be affected by Alzheimer's disease and memory impairment, these results are encouraging as they demonstrate the modifiability of this structure even later in life. A meta-analysis by Wilckens and colleagues further supports the claim that physical activity has a positive influence on the volume of the hippocampus after analyzing 23 exercise interventions.[122] Similar to the randomized controlled trials outlined above, follow-up analyses found that hippocampal volume significantly decreased by 0.72% among the control groups, while hippocampal volume increased by 1.2% among the exercise groups. While the increase among exercisers was not significant, these results support the hypothesis that exercise may attenuate or reverse atrophy of the hippocampus.[122]

As mentioned in Section 2.4 of this document, a benefit of physical activity is the potential to improve aspects of physical fitness.[53] It has been suggested that levels of physical fitness may attenuate the decline in volume seen in an aforementioned study.[37] Further, higher levels of cardiorespiratory fitness, along with physical activity, have been related to greater gray matter volumes in specific regions of the brain, including the hippocampus.[128] Although the hippocampus is one of the most readily studied areas of the brain, the basal ganglia may be also influenced by physical activity. In the first study to explore the relationship between aerobic fitness and the structure and function of the basal ganglia in humans, Chaddock and colleagues analyzed data from 55 children who were 9 and 10 years of age.[129] Results showed that children with higher

fitness levels, compared to those with lower fitness, performed better on the flanker task and had greater volumes of the dorsal striatum. In addition, there was an association found between aerobic fitness, volume of the dorsal striatum, and performance on the flanker test. These findings suggests that increased fitness is associated with another region of the brain responsible for cognitive function. While this study was conducted in children, these findings support that higher aerobic fitness levels impact the structure and function of areas of the brain beyond the hippocampus, such as the basal ganglia.[129] Across the spectrum of the lifespan, a study by Verstynen and colleagues assessed similar relationships in an older adult population through a 12-month randomized controlled trial involving an aerobic exercise intervention. They found a positive association between fitness level and the volume of the caudate nucleus and nucleus accumbens.[90]

Compared to those investigating gray matter volume, less studies have examined the influence of physical activity on white matter volume.[130] Cross-sectional evidence suggests a relationship exists between physical activity and improved white matter integrity.[131,132] Voss and colleagues reported findings from the physical activity intervention described above by Erickson and colleagues.[37,130,133] Using DTI, it was found that increased cardiorespiratory fitness was associated with increased white matter integrity as detected through increases in fractional anisotropy in white matter tracts connecting the frontal and temporal lobes.[133]

2.7.2 Brain Function and Physical Activity

In the current state of the literature, a major focus of functional findings has been within the prefrontal region of the brain.[39,40,125] Findings by Rosano and colleagues demonstrate this, where increased activation in prefrontal brain regions, important for executive control, was found in older adults who adhered to a multicomponent physical activity intervention for 2 years

following a 12-month intervention.[125] Similarly, Voss and colleagues found enhanced connectivity among the default mode network and frontal executive network following a 12-month PA intervention. Improved functional outcomes (both in studies supporting connectivity and activation) were also associated with improvements in executive control.[39] Colcombe and colleagues also found improvements in the functioning and recruitment of the frontal executive network in older adults within the aerobic exercise group following a 6-month intervention.[40]

2.7.3 Cognitive Function and Physical Activity

In general, many domains of cognitive function have shown to be improved following physical activity.[121] As mentioned in Section 2.7, the positive influence of physical activity on cognition may be seen following an acute bout of physical activity. This is supported by strong evidence in domains such as attention, memory, crystalized intelligence, processing speed, and executive control.[33] Among the many domains suggested to be improved by physical activity, executive function has shown the largest and most consistent changes. Proposed hypotheses for this evidence are similar to the influence of physical activity on brain volume in that certain aspects of cognition may be more sensitive than others.[128] Other domains shown to be improved by physical activity include visuospatial processing, learning and memory, spatial memory, and processing speed.[37,121,134] While a majority of research in this space involves aerobic physical activity interventions, a systematic review and meta-analysis by Northey and colleagues demonstrated that other modes of physical activity including aerobic, resistance, multicomponent, and tai chi exercise were also effective for improving cognitive function in older adults.[135]

Despite this encouraging evidence, the Lifestyle Interventions and Independence for Elders (LIFE) study provided alternative results. Sedentary older adults (ages 70-89 years) at high risk

for mobility disability with no diagnosis of dementia or cognitive impairment were included in this study. Participants were randomized to a multicomponent physical activity intervention or health education program. Physical activity levels were assessed with the CHAMPS questionnaire and the Actigraph accelerometer, both of which are validated for the older adult population.[136,137] In comparison to the health education program, the physical activity intervention did not result in improved cognition, or a reduced incidence of MCI or dementia, as hypothesized.[138]

2.7.4 Factors and Mechanisms of Neurocognition and Physical Activity

The proposed mechanisms in which physical activity influences brain health may operate separately or together through multiple pathways on different levels.[42,122,139] Physical activity has been shown to protect against chronic diseases as well as associated risk factors, as mentioned in Section 2.4.[33] Therefore, it is proposed that physical activity may influence the brain through peripheral processes including reduced inflammation, improved insulin sensitivity, and improved aspects of metabolic function (e.g., mitochondrial biogenesis/efficiency).[11]

A reduction in systemic inflammation has been seen with regular exercise. This may occur through the promotion of an anti-inflammatory response by reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines.[140] This is relevant to brain health as both age and dementia-related cognitive decline have been associated with pro-inflammatory markers in the blood.[141]

Physical activity has also contributed to improved insulin sensitivity and mitochondrial function.[142] While individuals performing higher levels of physical activity have higher levels of insulin sensitivity, it has also been shown to contribute to improved activation and of memory-related brain networks and similarly that domain of cognitive function.[102] These increased metabolic functions are believed to positively influence neural plasticity, structural integrity, and functional integrity of the brain.[40]

In addition to insulin signaling, neurotrophic factor signaling may be involved as well. At the basic level, biochemical changes have been induced by physical activity. These analytes are identified and measured from the bloodstream or cerebrospinal fluid. One of the most consistently found are increasing circulating levels of BDNF. Animal models have proposed that the role of BDNF is in the potentiation and proliferation of neurons in the brain.[143] Promising results have been shown in humans also, as BDNF has been associated with improved memory and volume of the hippocampus.[144] Other identified analytes, although less consistently in the literature, include IGF-1 and VEGF. It has been proposed that IGF may contribute to neurogenesis and angiogenesis while VEGF may contribute to the growth and survival of blood vessels.[143]

The aforementioned morphological changes to the structure and function of the brain may also be proposed mechanisms. A large majority of the literature in this space has focused on the influence of physical activity on gray matter volume, including the prefrontal cortex, hippocampus, basal ganglia, and other regions.[122] As elaborated upon in prior Sections (2.7.1), higher cardiorespiratory fitness has been associated with increased gray matter volume, where this morphology has been shown to mediate improved aspects of cognitive function.[90,134] These associations have shown to be regionally specific, as they have held in multiple areas of the brain such as the hippocampus and areas of the basal ganglia. [90,134]

Physical activity may also influence mechanisms at the psychosocial level through stress, sleep, mood, and pain.[42] Physical activity has been shown to improve perceived stress levels.[53] In consideration of brain health, physical activity may moderate the relationship between stress, hippocampal volume, and memory.[123] This relationship is believed to involve the role of physical activity in modulating cortisol and AMPK and BDNF, by-products of stress.[139] Improved sleep is another benefit of physical activity that may contribute to brain health.[53] Sleep efficiency has been shown to be a mediator in the relationship between physical activity and cognitive domains including working memory, switching, verbal ability, verbal fluency, recall.[145] Physical activity has also reportedly improve mood, depression, and anxiety.[53] However, these psychosocial factors, physical activity, and cognition are not yet fully understood due to large inconsistencies across the literature.[42]

There are limitations within the literature that promote caution when considering the above mechanisms. For example, physical activity parameters may have a differing effect on mechanisms. In addition, characteristics of the populations being studied, such as age groups across the lifespan, may be influenced differently by physical activity given the development or atrophy in the brain during those ages.[41]

2.8 Summary

There is variability in study design and quality, populations of interest, measurement tools, and intervention parameters to assess how obesity, weight loss, physical activity, and brain integrity are related.[122,139] Despite this heterogeneity, there are consistent findings from cross-sectional, longitudinal, and randomized controlled trials highlighting relationships between

obesity, physical activity, and the brain. Obesity contributes to poor neurocognitive outcomes such as an increased risk of dementia (specifically midlife obesity),[9,76-79,93] altered structure (specifically gray matter changes in hippocampus) and functional changes (specifically in areas of reward and feeding behaviors),[18] and impaired cognition (specifically executive function).[93,146] Consistencies in the physical activity literature include associations between physical activity and increased gray matter volume in specific areas of the brain such as the hippocampus and prefrontal cortex,[37,38,122,126,147] and improvements in executive function.[33]

Despite this convincing evidence, gaps and inconsistencies in the literature are largely centered on weight loss interventions for neurocognitive health. Gaps exist when considering the potential influence of intentional weight loss approaches on the structure, function, and cognitive function of the brain, and the mechanisms in which these occur. In addition, more literature is needed to assess the influence of obesity, weight loss, and physical activity on volume of the basal ganglia. Therefore, to address some of these questions, there is a clear need for studies with quality designs and techniques to promote a better understanding of the impact of obesity, weight loss, and physical activity on the brain. The purpose of the current analysis was to assess the influence of a 12-month standard behavioral weight loss intervention on aspects of brain health in adults with overweight or obesity.

3.0 Methods

The parent study (R01 HL096770; PI: Jakicic) was conducted to examine the effects of a behavioral weight loss intervention, involving varying doses of physical activity, on cardiovascular outcomes, with the primary outcome involving cardiac magnetic resonance imaging (CMR). An ancillary study (R01 DK095172; PI: Erickson) added a neuroimaging arm to the parent trial to examine the effects of weight loss and physical activity on aspects of brain integrity.

3.1 Methods from Parent and Ancillary Studies

3.1.1 Participants

Recruitment was conducted to identify eligible individuals to participate in the parent study. Three hundred eighty-three (383) participants across 16 cohorts satisfied the following inclusion and exclusion criteria for the parent study as previously described[148]:

Inclusion Criteria for Parent and Ancillary Study:

1. Aged 18 to 55 years
2. BMI of 25.0 to < 40.0 kg/m^2
3. Ability to provide informed consent
4. Ability to provide consent from personal physician
5. Ability to complete baseline graded exercise testing, followed by clearance from study physician after reviewing results from this testing

Exclusion Criteria for Parent and Ancillary Study:

1. Inability to provide informed consent
2. Member of household on study staff
3. Currently pregnant, currently lactating, breastfeeding in the past 3 months, or report a planned pregnancy within the next 12 months
4. History of bariatric surgery
5. Report current medical condition or treatment that could affect body weight such as cancer (of note: individuals previously diagnosed with non-melanoma skin cancers and/or successful treated for cancer and remained disease-free for five years or more were considered eligible), diabetes mellitus, hyperthyroidism, chronic renal insufficiency, chronic liver disease, gastrointestinal disorders (examples include ulcerative colitis, Crohn's disease, malabsorption syndrome, etc.), and others
6. Report current cardiovascular condition (e.g. congestive heart failure, angina, uncontrolled arrhythmia, etc.) or condition requiring chronic anticoagulation (examples include recent or recurrent DVT, etc.), symptoms suggesting an increased acute risk for a cardiovascular event, prior myocardial infarction, or coronary artery bypass grafting or angioplasty
7. Resting systolic blood pressure of >160 mmHg or resting diastolic blood pressure of >100 mmHg, taking medication for blood pressure control or those that may influence blood pressure or heart rate response to exercise (examples include beta blockers, etc.)

8. Report current eating disorders that are contraindications for weight loss or physical activity
9. Alcohol or substance abuse
10. Undergoing current treatment for psychological conditions (examples include depression, bipolar disorder, etc.), taking psychotropic medications within the previous 12 months, or hospitalized for depression within the past 5 years
11. Report performing exercise > 60 minutes per week over the past 3 months
12. Report weight loss of > 5% or current participation in a weight reduction diet in the past 3 months
13. Report plans to relocate to a location that is inaccessible to the study site, or report employment/personal/travel commitments that prohibit attendance to at last 80% of the scheduled intervention sessions and 100% of the scheduled assessments

Of the 383 recruited adults with overweight or obesity, 125 (32.6%) participated in the ancillary study. To do so, the following criteria were met as previously described[29,32,36]:

Exclusion Criteria specific to Ancillary Study:

1. History of or current neurological disorder (examples include dementia, stroke, etc.) or traumatic brain injury
2. Left-handedness
3. Metallic implants (of note: individuals with a history of welding work or tattoos containing metal filings were subject to further MRI safety screening)
4. Report claustrophobia

3.1.2 Recruitment, Screening, and Informed Consent

Recruitment resources were approved by the Institutional Review Board at the University of Pittsburgh. Strategies included newspaper and radio advertisements in addition to direct mailings. These methods included a phone number where interested individuals contacted study staff for further information. At this time, study staff provided a brief description of the study and the opportunity to participate in an initial phone screening to determine the potential for eligibility based upon the criteria previously described (see Section 3.1.1). All apparently eligible individuals were invited to an orientation session led by the principal investigator or designated co-investigator. Here, a detailed description of the study was provided with opportunity to ask any additional questions to ensure understanding of potential participation. Eligible individuals provided written informed consent if they agreed to participate in the study. In addition, eligible individuals were asked to complete a physical activity readiness questionnaire (PAR-Q) and a detailed medical history prior to proceeding with the study to assess eligibility and promote safety. To further minimize potential risks, participants sought medical clearance from their personal physician prior to proceeding. The study was approved by the Institutional Review Board at the University of Pittsburgh.

After that participant was deemed eligible to participant in the parent study, they were given the option of also enrolling in the ancillary study to examine brain and cognitive outcomes. For participants expressing interest, a description of the ancillary study was provided by an investigator and written informed consent was obtained. A safety assessment was conducted to determine eligibility for the MRI. This included a thorough interview to identify potential contraindications to undergoing an MRI scan. These factors are previously described (see Section 3.1.1, Exclusion Criteria specific to Ancillary Study).

3.1.3 Experimental Design and Randomization

Following the confirmation of eligibility, participants were randomized to one of three standard behavioral weight loss intervention conditions. A brief description of each group is as follows:

1. Diet-Only (DIET): Participants randomized to this group received only the diet and behavioral intervention components.
2. Diet + 150 minutes of physical activity (DIET + MOD-PA): Participants randomized to this group received the diet, behavioral, and physical activity intervention components. Physical activity volume was progressed to 150 minutes per week.
3. Diet + 250 minutes of physical activity (DIET + HIGH-PA): Participants randomized to this group received the diet, behavioral, and physical activity intervention components. Physical activity volume was progressed to 250 minutes per week.

3.1.4 Behavioral Weight Loss Intervention Components

The three components in this behavioral weight loss intervention included a dietary, behavioral, and physical activity component. As outlined above (see Section 3.1.3), all three potential randomization groups (DIET, DIET + MOD-PA, and DIET + HIGH-PA) received the dietary and behavioral intervention components. However, only the DIET + MOD-PA and DIET + HIGH-PA groups received the physical activity component of the intervention. Individual components of intervention conditions are described in detail below:

Diet: All groups (DIET, DIET + MOD-PA, DIET + HIGH-PA) were prescribed a calorie-restricted diet. Calorie goals were prescribed according to baseline body weight (< 90.7 kg = 1200 kcal/day; 90.7-113.4 kg = 1500 kcal/day; 113.4 kg > = 1800 kcal/day) and adjusted accordingly based on weight loss throughout the intervention. Prescriptions ranged from 1200-1800 kilocalories (kcal) per day, and a recommended reduction in fat intake to 20-30% of total kcals per day (<90.7 kg = 27-49 g/day; 90.7-113.4 kg = 33-50 g/day; 113.4 kg > = 40-60 kg/day). To assist in reaching these calorie and fat intake goals, meal plans were developed by registered dietitians. To further facilitate adherence, participants were encouraged to record their diet (calorie and fat intake) in a diary that was returned to intervention staff each week for review and feedback.

Behavioral Sessions: All intervention conditions (DIET, DIET + MOD-PA, DIET + HIGH-PA) received behavioral intervention sessions. Weeks 1-24 were in-person group sessions, while Weeks 25-52 were alternated in-person group and individual telephonic sessions. In-person and telephonic sessions were led by professionals with appropriate training in weight loss interventions.

In-person group sessions were conducted by specific randomization groups on the same day throughout the duration of the intervention. In-person sessions began with a measurement of body weight and the return of participant diaries, followed by a behavioral session that lasted approximately 30-60 minutes in duration. Intervention topics included strategies that promote engagement in intervention behaviors that promote weight loss, supported by paper-based and other lesson materials. If a participant missed a session, an abbreviated make-up session was offered at a time that was convenient for the participant. Further, if a participant was unable to attend a group or make-up session, intervention materials were mailed.

Individual telephonic sessions were alternated with in-person group sessions during Weeks 25-52. Calls lasted approximately 10 minutes in duration and were guided by a standard script to standardize the delivery and content of these sessions. Intervention topics included reinforcement of group session topics, barriers to engagement, adherence to intervention components, and others.

Physical Activity: Physical activity was prescribed to two of the three intervention groups (DIET + MOD-PA and DIET + HIGH-PA). The DIET group did not receive information about physical activity during the behavioral intervention sessions.

For the DIET + MOD-PA condition, physical activity was progressed to 150 minutes of physical activity per week. It was encouraged to break this activity into 5 days per week, with a progression in duration. Duration recommendations began at 20 minutes per day (100 min/week) and graduated to at least 30 minutes per day (150 min/week). This progression ramped by intervals of 5 minutes per day (25 minutes per week) every 4 weeks to promote adherence and safety. Participants were instructed to perform sessions in at least 10-minute bouts to contribute to the total prescribed amount.

For the DIET + HIGH-PA condition, physical activity was progressed to 250 minutes of physical activity per week. It was encouraged to break this activity into 5 days per week, with a progression in duration. Duration recommendations began at 20 minutes per day (100 min/week), graduating to at least 50 minutes per day (250 min/week). This progression ramped by intervals of 5 minutes per day (25 minutes per week) every 4 weeks to promote adherence and safety. Participants were instructed to perform sessions in at least 10-minute bouts to contribute to the total prescribed amount.

The above amounts of physical activity were instructed to be performed at a moderate-to-vigorous intensity. The intensity of physical activity was measured by the Borg 15-point RPE

scale, with moderate intensity ranging from RPEs of 13-15 on this scale.[149] Home-based aerobic-types of physical activity were performed to reach these prescribed volumes. Similar to dietary behaviors, participants in the DIET + MOD-PA and DIET + HIGH-PA groups were encouraged to record their physical activity levels in a diary that was returned to intervention staff each week for review and feedback.

3.1.4.1 Assessment Procedures

Data from the parent and ancillary studies were used to address the specific aims outlined in Section 1.3. Baseline assessments for the parent and ancillary studies were performed prior to randomization into intervention groups. Data from the parent study that are included in the analyses proposed here include measurements of body weight and physical activity levels. For the ancillary study, assessments included measurements of cognitive function and brain structure. These same assessment procedures were performed 12 months later after the culmination of the intervention. Whenever possible, measurement of body weight was assessed by study staff who were not involved in the delivery of the intervention, and when not possible, the staff were blinded to prior measurements of body weight. Physical activity was objectively measured and data were only analyzed by non-intervention staff. Staff performing measures of brain and cognition were not involved in the delivery of the intervention.

Body Weight: For assessment measurements of body weight, participants were clothed in a lightweight hospital gown with shoes removed. Weight was measured in duplicate using a calibrated digital scale (Tanita Digital Scale, Model #WB-110A) to the nearest 0.1 kilograms (kg), with duplicate measures differing by $\leq$0.2 kg.

Physical Activity: Physical activity was measured using the SenseWear Armband activity monitor (BodyMedia Inc). The monitor was placed on the upper arm by study staff, who instructed

participants on how to properly position the device. Participants were instructed to wear the armband for all waking hours for seven consecutive days. During this period, participants were encouraged to perform their regular behaviors. Data were considered valid if the wear time totaled to ≥ 10 hours per day for at least 4 days in that time period. Data were analyzed using proprietary algorithms developed by the manufacturer to classify each minute as light (>1.0 to <3.0 METS), moderate (3.0 to <6.0 METS), or vigorous intensity physical activity (≥6.0 METS). These data were then used to identify patterns of physical activity for light and moderate-to-vigorous intensity physical activity, which were then used for data analysis.

Cognitive Variables: Cognitive assessments were conducted to assess executive function and non-food-related reward processing. Tests included N-Back tasks, Task Switch, Stroop Color-Word Task, and Iowa Gambling Task (IGT), as previously reported by Peven and colleagues.[29] The N-back tasks were used for the analyses proposed below (Section 3.2). These tasks measure working memory function, which is a domain of executive function.

Brain Structure: As previously mentioned (Section 3.1.2), participants went through a safety screening for contraindications and were instructed to remove all metal artifacts. Magnetic resonance imaging (MRI) parameters and processing methods have been previously reported.[32,36] MRI was conducted using a Siemens 3.0 Tesla (3T) Verio MRI scanner (Magnetom Trio Tim Syngo). During scans, a 32-channel phased-array receiver imaging coil was placed around the head for radio frequency (RF) transmission and reception. To stabilize the receiver imaging coil and minimize movement during the scan, foam padding was placed within the head coil. MRI scan parameters for a high-resolution anatomical image included: a T1-weighted sequence, Magnetization-Prepared Rapid Acquisition of Gradient Echo (MPRAGE) imaging protocol, an acquisition matrix of 256 slices, a field-of-view (FOV) of 250 mm, voxels of 1 mm^3 (1 mm x 1mm

x 1mm), 192 slices collected from left to right (sagittal plane), a slice thickness of 1.0 mm, an echo time (TE) of 2.93 ms, a repetition time (TR) of 1900 ms, an inversion time (TI) of 900 ms, a flip angle of 9°, and a sequence duration of 4 minutes and 26 seconds. Functional MRI of the Brain (FMRIB)'s Integrated Registration and Segmentation Tool (FIRST) (FMRIB Software Library version 5.0.9) was used for segmentation and volumetric analysis of subcortical brain areas. This semi-automated model-based segmentation tool was employed to identify region-specific volumes in areas of the brain including the hippocampus and basal ganglia. Further detailed processing methodology has been previously reported.[36] Segmentations were visually checked for any errors.

3.2 Data Analysis

3.2.1 Statistical Analyses

Statistical analyses were performed using STATA software (StataSE, Version 15). Statistical significance was pre-determined at $p \leq 0.05$. For the parent study, an intent-to-treat approach was taken for analyses where all participants who enrolled and randomized in the ancillary trial were encouraged to complete follow-up assessments, regardless of status. However, for this secondary analysis, only participants with available data are included.

Multiple regression analyses were conducted to assess which variables influenced the hypothesized associations, as described in Section 1.4. The dependent or outcome variables, depending upon specific aim being tested, were cognitive variables, change in cognitive variables, gray matter volume of the hippocampus, gray matter volume of the basal ganglia, change in gray matter volume of the hippocampus, or change in gray matter volume of the basal ganglia. Change

variables were created by subtracting baseline values from 12-month values. Independent or predictor variables such as age, sex, and education were added into the models as covariates of interest due to potential correlations among the variables. In analyses for Specific Aims 3 and 4, body weight was used as a covariate of interest.

Descriptive analyses were performed to assess normality prior to analysis. Histograms and quantile-quantile plots were used to assess the distribution of each variable. Scatterplots were used to assess patterns present between the variables. If variables were not normally distributed, transformations or non-parametric tests were considered.

Assumptions to multiple regressions were checked using histograms and scatterplots. Collinearity, interactions, and confounding were checked to satisfy assumptions. Outliers and influential points were checked using calculations and plots. If present, a refit of the regression model was considered. Transformation or refit of the model without influential points were performed if the statistical significance of the association was altered.

4.0 Results

4.1 Participant Characteristics

Of the 383 recruited adults with overweight or obesity, 125 (32.6%) participated in the ancillary study. The final sample included 115 individuals who completed both pre (baseline) and post-intervention (12-months) assessments, with missing data attributed by select assessments or dropout. Baseline characteristics of this sample are outlined in Table 1. Continuous variables are presented as median and interquartile range (25^{th} percentile, 75^{th} percentile). Categorical variables are presented by count and percent.

Table 1 Baseline Characteristics for Ancillary Study Participants (n=115)

Characteristics	**Median [IQR]** or **n (%)**
Age (years)	48 [42, 52]
BMI (kg/m^2)	32.43 [28.99, 35.4]
Weight (kg)	89.95 [79.4, 99.8]
Education	
Did Not Finish Elementary School	0 (0%)
Finished Middle School (8th grade)	0 (0%)
Finished Some High School	1 (0.87%)
High School Graduate or G.E.D.	4 (3.48%)
Vocational or Training School after High School	5 (4.35%)
Some College or Associate degree	21 (18.26%)
College Graduate or Baccalaureate Degree	46 (40.00%)
Masters or Doctoral Degree (PhD, MD, JD, etc.)	38 (33.04%)
Ethnicity (Hispanic/Latino)	1 (0.87%)
Race (Caucasian/White)	89 (77.39%)
Sex (Female)	89 (77.39%)

Note: IQR = Interquartile Range (25th percentile, 75th percentile)

Table 2 includes median sample values at baseline and 12-months of independent and dependent variables involved in the analyses to test the specific aims of this study. There was a significant loss of body weight from pre- to post-intervention ($p<0.001$). In addition, there was a significant improvement in volumes of both low-intensity ($p<0.001$) and moderate-to-vigorous physical activity ($p<0.001$). The only cognitive or volumetric outcomes that demonstrated a significant difference from pre- to post-intervention included N-back measurements of One-Back Reaction Time ($p=0.0155$) and Two-Back Reaction Time ($p = 0.0064$), with both having a decrease in time from baseline to 12-months.

Table 2 Summary from Baseline to 12-Months in Body Weight, Physical Activity, Cognitive, and Volumetric Variables

Variables	Median [IQR] at Baseline	Median [IQR] at 12-Months	p-value
Body Weight (kg)	89.95 [79.4, 99.8]	80.30 [69.2, 90.1]	< **0.001**
Light-Intensity Physical Activity (MET-min/wk)	2476.87 [1716.10, 3401.04]	3035.45 [2014.16, 4245.06]	< **0.001**
Moderate-to-Vigorous-Intensity Physical Activity (MET-min/wk)	879.17 [445.96, 1637.48]	1337.03 [841.13, 2603.06]	< **0.001**
One-Back Reaction Time (ms)	864.91 [748.02, 952.64]	828.17 [720.44, 982.43]	**0.0155**
Two-Back Reaction Time (ms)	1038.92 [911.32, 1163.15]	1021.59 [898.40, 1129.67]	**0.0064**
Reaction Time Difference (ms)	177.11 [88.49, 252.27]	169.15 [72.21, 257.10]	0.4362
Reaction Time Difference % Change	20.04 [9.45, 30.18]	19.11 [7.24, 29.39]	0.5427
One-Back Accuracy Score	0.96 [0.89, 0.98]	0.96 [0.89, 0.98]	0.6750
Two-Back Accuracy Score	0.86 [0.69, 0.93]	0.86 [0.76, 0.93]	0.0902
Accuracy Difference Score	-0.07 [-0.18, -0.02]	-0.07 [-0.13, -0.005]	0.1538
Accuracy Difference % Change Score	-8.16 [-20.27, -2.60]	-8.16 [-14.29, -0.70]	0.1532
Collapsed Accumbens Volume (mm^3)	925.06 [790.60, 1035.69]	913.62 [6002.43, 7006.65]	0.3322
Collapsed Caudate Volume (mm^3)	6576.54	6547.93	0.6392
Collapsed Hippocampus Volume (mm^3)	7537.84 [7053.38, 8054.73]	7477.76 [7101.06, 7941.25]	0.7043
Collapsed Pallidum Volume (mm^3)	3382.68 [3191.95, 3686.91]	3366.47 [3189.09, 3561.97]	0.1358
Collapsed Putamen Volume (mm^3)	9608.27 [8916.86, 10275. 84]	9552.02 [8913.99, 10208.13]	0.2667

***Reaction Time and Accuracy Difference computed as two-back reaction time minus one-back reaction time*
Note: p-value from Wilcoxon Signed Rank Test. Bolded text indicates a p-value < 0.05

4.1.1 Associations Between N-Back Reaction Time Outcomes and Body Weight at Baseline

Table 3 presents the model output estimating the relationship between body weight and N-back reaction time outcomes at baseline. The N-Back reaction time outcomes included one-back reaction time, two-back reaction time, reaction time difference score, and reaction time difference percent change score. Unadjusted models included body weight as the independent variable, while adjusted models included age, sex, and education.

In the unadjusted analysis, baseline body weight was not significantly associated with baseline one-back reaction time (p=0.736). Body weight remained not significantly associated with one-back reaction time in the adjusted analysis. However, in the adjusted analysis, age was positively associated with one-back reaction time (p=0.001). Similarly, in the unadjusted analysis, baseline body weight was not significantly associated with baseline two-back reaction time, and body weight remained not significantly associated with two-back reaction time in the adjusted analysis. However, similar to the one-back analysis, age was significantly associated with two-back reaction time (p=0.000).

Analyses were also conducted to examine the association between body weight and the difference between the one-back and two-back reaction times, with analyses conducted on the absolute difference and the percent difference. The absolute difference score at baseline was not significantly associated with baseline body weight in either the unadjusted (p=0.297) or adjusted (p=0.542) analysis, with a similar pattern observed for the analyses of the percent difference score at baseline (unadjusted analysis p=0.265, adjusted analysis p=0.600). Unlike the separate analyses for the one-back and two-back reaction times, none of the covariates were significantly associated with the absolute or percent difference scores.

Table 3 Association Between Body Weight and N-Back Reaction Time Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
One-Back Reaction Time	Intercept	906.0364	97.0375	0.000	0.0010	700.0031	159.6136	0.000	0.1235
	Weight (kg)	-0.3562	1.0551	0.736		-0.4111	1.1169	0.714	
	*Age (years)	-----	-----	-----		5.6559	1.7168	0.001	
	*Sex (female)	-----	-----	-----		-22.7236	37.4126	0.545	
	*Education (College degree or higher)	-----	-----	-----		-37.9604	32.4585	0.245	
Two-Back Reaction Time	Intercept	1160.065	99.6689	0.000	0.0116	856.2496	163.1395	0.000	0.1413
	Weight (kg)	-1.2490	1.0837	0.252		-0.9984	1.1416	0.384	
	*Age (years)	-----	-----	-----		6.6190	1.7547	0.000	
	*Sex (female)	-----	-----	-----		-5.2553	38.2390	0.891	
	*Education (College degree or higher)	-----	-----	-----		-20.3872	33.1755	0.540	
**Reaction Time Difference Score	Intercept	254.0185	78.3816	0.002	0.0096	156.2466	137.1208	0.257	0.0172
	Weight (kg)	-0.8928	0.8522	0.297		-0.5873	0.9595	0.542	
	*Age (years)	-----	-----	-----		0.9631	1.4748	0.515	
	*Sex (female)	-----	-----	-----		17.4682	32.1404	0.588	
	*Education (College degree or higher)	-----	-----	-----		17.5731	27.8845	0.530	
Reaction Time Difference Percent Change Score	Intercept	30.2015	9.9563	0.003	0.0073	21.9764	17.418	0.210	0.0148
	Weight (kg)	-0.0985	0.1083	0.365		-0.0641	0.1219	0.600	
	*Age (years)	-----	-----	-----		0.0303	0.1873	0.872	
	*Sex (female)	-----	-----	-----		2.14405	4.0827	0.601	
	*Education (College degree or higher)	-----	-----	-----		2.8425	3.5421	0.424	

*Variable was forced in the model as covariate for the adjusted analysis

**Reaction Time Difference computed as two-back reaction time minus one-back reaction time

4.1.2 Associations Between N-Back Accuracy Outcomes and Body Weight at Baseline

Table 4 presents the findings estimating the relationship between body weight and N-back accuracy outcomes at baseline. The N-Back accuracy outcomes included one-back accuracy score, two-back accuracy, accuracy score difference, and accuracy difference percent change score. Unadjusted models included body weight as the independent variable, while adjusted models included age, sex, and education.

In the unadjusted analysis, baseline body weight was not significantly associated with baseline one-back accuracy (p=0.579). After the addition of covariates into the adjusted analysis, body weight was not significantly associated with one-back accuracy score (p=0.584). Similar patterns were seen while evaluating two-back accuracy score, where baseline body weight nor any covariates were significantly associated with this cognitive outcome variable in the unadjusted and adjusted models. However, similar to the one-back analysis, age was significantly associated with two-back reaction time (p=0.000).

Analyses were also conducted to examine the association between body weight and the absolute and percent difference scores between one-back and two-back accuracy. The absolute difference score was not significantly associated with body weight in either the unadjusted (p=0.701) or adjusted (p=0.634) analyses, with a similar pattern observed for the analysis of the percent difference score (unadjusted analysis p=0.560, adjusted analysis p=0.616). None of the covariates were significantly associated in the either adjusted model testing for a relationship with absolute or percent difference scores.

Table 4 Association Between Body Weight and N-Back Accuracy Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
One-Back Accuracy	Intercept	0.9731	0.1246	0.000	0.0027	1.1372	0.2142	0.000	0.0445
	Weight (kg)	-0.0008	0.0014	0.579		-0.0008	0.0015	0.584	
	*Age (years)	-----	-----	-----		-0.0042	0.0023	0.074	
	*Sex (female)	-----	-----	-----		0.0061	0.0502	0.904	
	*Education (College degree or higher)	-----	-----	-----		0.0357	0.0436	0.414	
Two-Back Accuracy	Intercept	0.9061	0.1403	0.000	0.0043	1.1010	0.2405	0.000	0.0513
	Weight (kg)	-0.0011	0.0015	0.485		-0.0013	0.0017	0.454	
	*Age (years)	-----	-----	-----		-0.0047	0.0026	0.073	
	*Sex (female)	-----	-----	-----		-0.0055	0.0564	0.923	
	*Education (College degree or higher)	-----	-----	-----		0.0533	0.0489	0.000	
**Accuracy Difference Score	Intercept	-0.0670	0.0752	0.375	0.0013	-0.0362	0.1316	0.784	0.0088
	Weight (kg)	-0.0003	0.0008	0.701		-0.0004	0.0009	0.634	
	*Age (years)	-----	-----	-----		-0.0005	0.0014	0.716	
	*Sex (female)	-----	-----	-----		-0.0115	0.0308	0.709	
	*Education (College degree or higher)	-----	-----	-----		0.0176	0.0267	0.512	
Accuracy Difference Percent Change Score	Intercept	-2.9407	11.4869	0.798	0.0030	-3.3889	20.1184	0.867	0.0083
	Weight (kg)	-0.0731	0.1249	0.560		-0.0709	0.1408	0.616	
	*Age (years)	-----	-----	-----		-0.0366	0.2164	0.866	
	*Sex (female)	-----	-----	-----		-0.2205	4.7156	0.963	
	*Education (College degree or higher)	-----	-----	-----		2.8459	4.0912	0.488	

*Variable was forced in the model as covariate for the adjusted analysis

**Accuracy Difference computed as two-back accuracy minus one-back accuracy

4.1.3 Associations Between Change in N-Back Reaction Time and Accuracy Outcomes and Change in Body Weight

Analyses in Table 5 and 6 were conducted to assess the association between change in body weight and cognitive outcomes from pre- to post-intervention. Therefore, change in continuous variables were created by subtracting baseline values from 12-month values. Table 5 highlights the findings related to change in N-Back reaction time while Table 6 is dedicated to change in N-Back accuracy score.

In Table 5, both unadjusted (p=0.496) and adjusted (p=0.858) models revealed a non-significant association between change in body weight and change in one-back reaction time. Regardless of the addition of covariates, which were also non-significant, statistically significant relationships were not seen between change in body weight and change in two-back reaction time in either unadjusted (p=0.965) or adjusted (p=0.749) models. When evaluating the association between change in reaction time difference score and change in body weight, the unadjusted model was not significant (p=0.519). However, in the adjusted model, the covariate representing sex was significant (p=0.007). Lastly, change in body weight was not significantly (p=0.668) associated with the percent change in reaction time difference, and this held after the addition of covariates (p=0.430).

In Table 6, none of the independent variables, including body weight, were significantly associated with change in one-back accuracy, two-back accuracy, absolute accuracy difference, or percent accuracy difference.

Table 5 Association Between Change in Body Weight and Change in N-Back Reaction Time Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in One-Back Reaction Time	Intercept	-24.2921	25.8625	0.350	0.0042	51.0391	108.1718	0.638	0.0439
	Change in Weight (kg)	1.4023	2.0482	0.495		0.3814	2.1216	0.858	
	*Age (years)	-----	-----	-----		-1.9976	1.9336	0.304	
	*Sex (female)	-----	-----	-----		51.2799	40.1748	0.205	
	*Education (College degree or higher)	-----	-----	-----		-47.7134	36.18591	0.190	
Change in Two-Back Reaction Time	Intercept	-41.2682	25.0821	0.103	0.0000	141.6148	104.8904	0.180	0.0402
	Change in Weight (kg)	-0.0876	1.9864	0.965		0.6594	2.0572	0.749	
	*Age (years)	-----	-----	-----		-2.1343	1.8749	0.257	
	*Sex (female)	-----	-----	-----		-69.9832	38.9561	0.075	
	*Education (College degree or higher)	-----	-----	-----		-32.7546	35.0882	0.353	
**Change in Reaction Time Difference Score	Intercept	-16.9761	29.0469	0.560	0.0037	90.5757	119.8095	0.451	0.0698
	Change in Weight (kg)	-1.4899	2.3004	0.519		0.2780	2.3498	0.906	
	*Age (years)	-----	-----	-----		-0.1366	2.1416	0.949	
	*Sex (female)	-----	-----	-----		-121.2631	44.4970	0.007	
	*Education (College degree or higher)	-----	-----	-----		14.9589	119.8095	0.451	
Change in Reaction Time Difference Percent Change Score	Intercept	-25.7650	4.4759	0.000	0.0017	-0.6441	18.8530	0.973	0.0390
	Change in Weight (kg)	0.1537	0.3570	0.668		0.2918	0.3687	0.430	
	*Age (years)	-----	-----	-----		-0.1959	0.3365	0.562	
	*Sex (female)	-----	-----	-----		-11.8244	7.0475	0.096	
	*Education (College degree or higher)	-----	-----	-----		-7.7209	6.2911	0.222	

*Variable was forced in the model as covariate for the adjusted analysis

**Reaction Time Difference computed as two-back reaction time minus one-back reaction time

Table 6 Association Between Change in Body Weight and Change in N-Back Accuracy Outcomes

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in One-Back Accuracy	Intercept	0.0398	0.0465	0.394	0.0129	0.1489	0.1962	0.449	0.0378
	Change in Weight (kg)	0.0046	0.0037	0.229		0.0052	0.0038	0.177	
	*Age (years)	-----	-----	-----		0.0003	0.0035	0.936	
	*Sex (female)	-----	-----	-----		-0.0565	0.07285	0.440	
	*Education (College degree or higher)	-----	-----	-----		-0.0964	0.0656	0.145	
Change in Two-Back Accuracy	Intercept	0.0421	0.0975	0.667	0.0003	-0.3312	0.4145	0.426	0.0086
	Change in Weight (kg)	-0.0015	0.0077	0.850		-0.0021	0.0081	0.796	
	*Age (years)	-----	-----	-----		0.0055	0.0074	0.462	
	*Sex (female)	-----	-----	-----		0.0910	0.1539	0.555	
	*Education (College degree or higher)	-----	-----	-----		0.0646	0.1387	0.642	
**Change in Accuracy Difference Score	Intercept	0.0023	0.1075	0.983	0.0043	-0.4801	0.4548	0.294	0.0216
	Change in Weight (kg)	-0.0059	0.0085	0.488		-0.0073	0.0089	0.413	
	*Age (years)	-----	-----	-----		0.0052	0.0081	0.524	
	*Sex (female)	-----	-----	-----		0.1475	0.1689	0.384	
	*Education (College degree or higher)	-----	-----	-----		0.1610	0.1522	0.292	
Change in Accuracy Difference Percent Change Score	Intercept	-0.4134	3.7711	0.275	0.0140	13.5113	15.9828	0.400	0.0391
	Change in Weight (kg)	-0.3757	0.3008	0.214		-0.4667	0.3126	0.138	
	*Age (years)	-----	-----	-----		-0.4143	0.2853	0.149	
	*Sex (female)	-----	-----	-----		3.2886	5.9746	0.583	
	*Education (College degree or higher)	-----	-----	-----		-3.2335	5.3333	0.546	

*Variable was forced in the model as covariate for the adjusted analysis

**Accuracy Difference computed as two-back accuracy minus one-back accuracy

4.1.4 Associations Between Baseline Volumetric Outcomes and Baseline Body Weight

Results of the analyses to examine the associations between baseline body weight and baseline volumes of specific brain regions are shown in Table 7. Areas of the basal ganglia are represented by collapsed volumes of the nucleus accumbens, caudate nucleus, pallidum, and putamen. Body weight was not significantly related to collapsed volumes of the nucleus accumbens or caudate in either unadjusted ($p=0.273$ and $p=0.137$, respectively) or adjusted ($p=0.572$ and $p=0.303$, respectively) models. Accompanying covariates were not significantly related in adjusted models for either outcome variable.

The association between baseline collapsed volume of the hippocampus and baseline body weight was not associated in either the unadjusted ($p=0.580$) or adjusted ($p=0.724$) models. However, when added to the association, sex (female) was approaching significance ($\beta=-394.2906$, $p=0.054$). Sex (female) was also significant in the adjusted model for the baseline collapsed volume of the pallidum, while baseline body weight and all other covariates remained non-significant. Lastly, baseline body weight was not significantly associated with collapsed volumes of the putamen in unadjusted ($p=0.241$) or adjusted ($p=0.903$) models. However, age ($\beta=-24.1040$, $p=0.025$) and sex ($\beta=-599.2419$, $p=0.011$) were significant.

Table 7 Association Between Body Weight and Volumetric Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Collapsed Accumbens Volume	Intercept	790.7415	116.0185	0.000	0.0106	911.4601	202.3827	0.000	0.0238
	Weight (kg)	1.3905	1.2615	0.273		0.8032	1.4162	0.572	
	*Age (years)	-----	-----	-----		-0.9578	2.1768	0.661	
	*Sex (female)	-----	-----	-----		-48.0454	47.4374	0.313	
	*Education (College degree or higher)	-----	-----	-----		18.1510	41.1559	0.660	
Collapsed Caudate Volume	Intercept	5904.247	500.6174	0.000	0.0195	6587.389	857.8284	0.000	0.0664
	Weight (kg)	8.1561	5.4432	0.137		6.2167	6.0026	0.303	
	*Age (years)	-----	-----	-----		-12.6962	9.2266	0.172	
	*Sex (female)	-----	-----	-----		-154.8548	201.0704	0.443	
	*Education (College degree or higher)	-----	-----	-----		257.9337	174.4453	0.142	
Collapsed Hippocampus Volume	Intercept	7267.035	500.6223	0.000	0.0027	8331.766	864.0819	0.000	0.0366
	Weight (kg)	3.0175	5.4432	0.580		-2.1445	6.0464	0.724	
	*Age (years)	-----	-----	-----		-5.7410	9.2939	0.538	
	*Sex (female)	-----	-----	-----		-394.2906	202.5361	0.054	
	*Education (College degree or higher)	-----	-----	-----		-41.3196	175.717	0.815	
Collapsed Pallidum Volume	Intercept	3150.328	215.6839	0.000	0.0181	3732.613	357.747	0.000	0.1240
	Weight (kg)	3.3819	2.3451	0.152		0.0505	2.5033	0.984	
	*Age (years)	-----	-----	-----		-2.5963	3.8478	0.501	
	*Sex (female)	-----	-----	-----		-279.8545	83.8540	0.001	
	*Education (College degree or higher)	-----	-----	-----		74.9952	72.7503	0.305	
Collapsed Putamen Volume	Intercept	8938.597	588.6189	0.000	0.0121	11207.79	985.2308	0.000	0.1025
	Weight (kg)	7.5389	6.4000	0.241		-0.83867	6.8942	0.903	
	*Age (years)	-----	-----	-----		-24.1040	10.5969	0.025	
	*Sex (female)	-----	-----	-----		-599.2419	230.9328	0.011	
	*Education (College degree or higher)	-----	-----	-----		66.3700	200.3534	0.741	

*Variable was forced in the model as covariate for the adjusted analysis

4.1.5 Associations Between Change in Volumetric Outcomes and Change in Body Weight

Analyses were performed to assess the associations between body weight and volumetric outcomes from pre- to post-intervention, with results shown in Table 8. Change was calculated by subtracting baseline values from 12-month values. Change in body weight was not significantly associated with change in collapsed volumes of the nucleus accumbens (p=0.240), caudate nucleus (p=0.822), or hippocampus (p=0.977) across unadjusted models. This same relationship held through the addition of covariates in adjusted models for the collapsed volumes of the nucleus accumbens (p=0.509), caudate nucleus (p=0.906), or hippocampus (p=0.839).

There was a significant association between change in collapsed pallidum volume and body weight (p=0.032). The association remained significant (p=0.046) after adjusting for the covariates of age, sex, and education. The association between change in collapsed volume of the putamen and change in body weight was not statistically significant in either unadjusted (p=0.388) and adjusted models (p=0.748). In the adjusted model, sex (female) was approaching significance (p=0.066).

Additional exploratory analyses were conducted to examine the associations between percent change of these same variables (Appendix, Table 23). These exploratory analyses found similar results, with no statistically significant associations in unadjusted or adjusted models between percent change in body weight activity and percent change in volumes of the nucleus accumbens, caudate nucleus, hippocampus, or putamen. However, the association between percent change in body weight and percent change in the volume of the pallidum remained statistically significant in both unadjusted (p = 0.030) and adjusted (p = 0.045) models.

Table 8 Association Between Change in Body Weight and Change in Volumetric Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in Collapsed Accumbens Volume	Intercept	-33.27844	22.4555	0.141	0.0123	4.7333	94.024	0.960	0.0496
	Change in Weight (kg)	-2.1017	1.778	0.240		-1.2212	1.8441	0.509	
	*Age (years)	-----	-----	-----		-0.1654	1.6807	0.922	
	*Sex (female)	-----	-----	-----		-59.4566	34.9204	0.091	
	*Education (College degree or higher)	-----	-----	-----		33.8828	31.4532	0.284	
Change in Collapsed Caudate Volume	Intercept	-69.0009	80.1974	0.391	0.0005	-197.2242	341.6239	0.565	0.0046
	Change in Weight (kg)	-1.4333	6.3514	0.822		-0.7968	6.7002	0.906	
	*Age (years)	-----	-----	-----		2.3081	6.1066	0.706	
	*Sex (female)	-----	-----	-----		-21.4766	126.8785	0.866	
	*Education (College degree or higher)	-----	-----	-----		63.7828	114.2809	0.578	
Change in Collapsed Hippocampus	Intercept	-36.5944	88.5986	0.680	0.0000	-278.321	374.5853	0.459	0.0190
	Change in Weight (kg)	0.1992	7.0167	0.977		1.4932	7.3467	0.839	
	*Age (years)	-----	-----	-----		3.7616	6.6957	0.575	
	*Sex (female)	-----	-----	-----		-48.5462	139.1203	0.728	
	*Education (College degree or higher)	-----	-----	-----		166.9617	125.3072	0.186	
Change in Collapsed Pallidum	Intercept	-94.8454	35.3241	0.008	0.0402	-179.0187	150.529	0.237	0.0434
	Change in Weight (kg)	-6.0589	2.7975	0.032		-5.9503	2.9523	0.046	
	*Age (years)	-----	-----	-----		1.5902	2.6907	0.556	
	*Sex (female)	-----	-----	-----		5.7431	55.9062	0.918	
	*Education (College degree or higher)	-----	-----	-----		11.6924	50.3554	0.817	
Change in Collapsed Putamen	Intercept	-118.6082	87.1593	0.176	0.0067	77.3823	364.9758	0.832	0.0440
	Change in Weight (kg)	-5.9784	6.9027	0.388		-2.3072	7.1582	0.748	
	*Age (years)	-----	-----	-----		-0.7674	6.5240	0.907	
	*Sex (female)	-----	-----	-----		-251.2915	135.5514	0.066	
	*Education (College degree or higher)	-----	-----	-----		98.2569	122.0926	0.423	

*Variable was forced in the model as covariate for the adjusted analysis

4.1.6 Associations Between Light-Intensity Physical Activity and Cognitive Outcomes at Baseline

The baseline associations between light-intensity physical activity and N-Back outcomes are shown in Table 9 (associations with reaction time outcomes) and Table 10 (accuracy outcomes). Baseline volume of light-intensity physical activity was not significantly associated with any reaction time outcomes in unadjusted or adjusted analyses. However, age was a significant covariate in the adjusted models with one-back reaction time (β=6.1669, p=0.001) and two-back reaction time (β=7.2726, p<0.001).

Light-intensity physical activity was not significantly associated with one-back or two-back accuracy in either the adjusted or unadjusted analyses. However, age approached statistical significance in the adjusted model with one-back accuracy (β=-0.0043, p=0.072) and was significant in two-back accuracy (β=-0.0056, p=0.006) analyses. Light-intensity physical activity was significantly associated with accuracy difference percent change score in the unadjusted analysis (β=-0.0027, p=0.022) and the adjusted analysis (β=-0.0028, p=0.021).

Table 9 Association Between Light-Intensity Physical Activity and N-Back Reaction Time Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
One-Back Reaction Time	Intercept	818.9245	35.8568	0.000	0.0239	591.651	163.7942	0.000	0.1517
	LPA (MET-min/wk)	0.0203	0.0123	0.102		0.0163	0.0121	0.180	
	*Body Weight (kg)	-----	-----	-----		-0.2539	1.1102	0.820	
	*Age (years)	-----	-----	-----		6.1669	1.7197	0.001	
	*Sex (female)	-----	-----	-----		5.5416	38.4543	0.886	
	*Education (College degree or higher)	-----	-----	-----		-33.7224	31.2225	0.296	
Two-Back Reaction Time	Intercept	1022.814	37.8929	0.000	0.0037	815.625	169.9389	0.000	0.1655
	LPA (MET-min/wk)	0.0083	0.01303	0.523		0.0051	0.0126	0.688	
	*Body Weight (kg)	-----	-----	-----		-1.1433	1.1518	0.323	
	*Age (years)	-----	-----	-----		7.2726	1.7842	0.000	
	*Sex (female)	-----	-----	-----		5.1879	39.8969	0.897	
	*Education (College degree or higher)	-----	-----	-----		-21.8535	33.3193	0.513	
**Reaction Time Difference Score	Intercept	203.8898	29.2717	0.000	0.0126	223.974	142.1773	0.118	0.0298
	LPA (MET-min/wk)	-0.0120	.0101	0.237		-0.0113	0.0105	0.286	
	*Body Weight (kg)	-----	-----	-----		-0.8894	0.9637	0.358	
	*Age (years)	-----	-----	-----		1.1058	1.4927	0.460	
	*Sex (female)	-----	-----	-----		-0.3538	33.3792	0.992	
	*Education (College degree or higher)	-----	-----	-----		11.8689	27.8762	0.671	
Reaction Time Difference Percent Change Score	Intercept	25.7956	3.6815	0.000	0.0171	31.9957	17.9219	0.077	0.0300
	LPA (MET-min/wk)	-0.0018	0.0013	-0.167		-0.0016	0.0013	0.217	
	*Body Weight (kg)	-----	-----	-----		-0.1083	0.1215	0.375	
	*Age (years)	-----	-----	-----		0.0491	0.1882	0.795	
	*Sex (female)	-----	-----	-----		-0.5001	4.2076	0.906	
	*Education (College degree or higher)	-----	-----	-----		2.0149	3.5139	0.568	

*Variable was forced in the model as covariate for the adjusted analysis

**Reaction Time Difference computed as two-back reaction time minus one-back reaction time

Note: LPA = Light-Intensity Physical Activity

Table 10 Association Between Light-Intensity Physical Activity and N-Back Accuracy Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
One-Back Accuracy	Intercept	0.8892	0.0473	0.000	0.0010	1.1169	0.2263	0.000	0.0482
	LPA (MET-min/wk)	$5.31e^{-06}$	$1.63e^{-05}$	0.745		1.06^{-05}	$1.67e^{-05}$	0.527	
	*Body Weight (kg)	-----	-----	-----		-0.0009	0.0015	0.573	
	*Age (years)	-----	-----	-----		-0.0043	0.0024	0.072	
	*Sex (female)	-----	-----	-----		0.0081	0.0531	0.879	
	*Education (College degree or higher)	-----	-----	-----		0.0387	0.0444	0.386	
Two-Back Accuracy	Intercept	0.8502	0.0532	0.000	0.0062	1.1004	0.1894	0.000	0.1071
	LPA (MET-min/wk)	$1.52e^{-05}$	$1.83e^{-05}$	0.409		$-2.07e^{-05}$	$1.4e^{-05}$	0.144	
	*Body Weight (kg)	-----	-----	-----		-0.9956	0.00123	0.972	
	*Age (years)	-----	-----	-----		-0.0056	0.0020	0.006	
	*Sex (female)	-----	-----	-----		-0.0297	0.0444	0.506	
	*Education (College degree or higher)	-----	-----	-----		0.0311	0.0372	0.405	
#** Accuracy Difference Score	Intercept	-3.0049	0.6584	0.001	0.0387	-2.2896	5.0612	0.662	0.0808
	LPA (MET-min/wk)	0.0002	0.0003	0.482		0.0002	0.0004	0.678	
	*Body Weight (kg)	-----	-----	-----		-0.0022	0.0399	0.952	
	*Age (years)	-----	-----	-----		-0.0055	0.0319	0.867	
	*Sex (female)	-----	-----	-----		0.1280	0.8816	0.888	
	*Education (College degree or higher)	-----	-----	-----		-0.3834	0.7486	0.621	
## Accuracy Difference Percent Change Score	Intercept	-3.8623	3.3291	0.249	0.0474	7.0606	16.1327	0.663	0.0752
	LPA (MET-min/wk)	-0.0027	0.0011	0.022		-0.0028	0.0012	0.021	
	*Body Weight (kg)	-----	-----	-----		-0.0203	0.1092	0.853	
	*Age (years)	-----	-----	-----		-0.1662	0.1691	0.328	
	*Sex (female)	-----	-----	-----		-4.0709	3.7709	0.283	
	*Education (College degree or higher)	-----	-----	-----		2.6632	3.1940	0.406	

*Variable was forced in the model as covariate for the adjusted analysis
**Accuracy Difference computed as two-back accuracy minus one-back accuracy
#Variable was log-transformed in the model
##Influential points were removed from variable
Note: LPA = Light-Intensity Physical Activity

4.1.7 Associations Between Moderate-to-Vigorous-Intensity Physical Activity and Cognitive Outcomes at Baseline

Volume of moderate-to-vigorous physical activity at baseline was not significantly associated with any reaction time outcomes in unadjusted or adjusted analyses, as shown in Table 11. This lack of a significant association held in the unadjusted and adjusted models with one-back accuracy and two-back accuracy outcomes in Table 12. When considering the associations with accuracy difference score, moderate-to-vigorous physical activity volume was not significantly associated in the unadjusted model (p=0.305). However, when the covariates for body weight, age, sex, and level of education were added into the adjusted model, the association became significant (β=-3.26e^{-05}, p=0.016). A similar pattern was found in the analyses of the accuracy difference percent score, where the association was not significant in the unadjusted analysis but became significant in the adjusted analysis (β=-0.0033, p=0.038).

Table 11 Association Between Moderate-to-Vigorous-Intensity Physical Activity and N-Back Reaction Time Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
One-Back Reaction Time	Intercept	867.1571	20.5584	0.000	0.0014	606.9158	177.8041	0.001	0.1395
	MVPA (MET-min/wk)	0.0043	0.0109	0.691		0.0067	0.0127	0.603	
	*Body Weight (kg)	-----	-----	-----		-0.1313	1.1583	0.910	
	*Age (years)	-----	-----	-----		6.3617	1.7504	0.000	
	*Sex (female)	-----	-----	-----		8.4792	46.6851	0.856	
	*Education (College degree or higher)	-----	-----	-----		-37.6200	32.1927	0.245	
Two-Back Reaction Time	Intercept	1045.738	21.5198	0.000	0.0000	824.1122	183.2869	0.000	0.1643
	MVPA (MET-min/wk)	-0.0006	0.0114	0.960		0.0015	0.0131	0.912	
	*Body Weight (kg)	-----	-----	-----		-1.1198	1.1940	0.350	
	*Age (years)	-----	-----	-----		7.3208	1.8044	0.000	
	*Sex (female)	-----	-----	-----		4.7886	48.1247	0.921	
	*Education (College degree or higher)	-----	-----	-----		-23.1453	33.1854	0.487	
**Reaction Time Difference Score	Intercept	178.5809	16.6752	0.000	0.0028	217.1964	153.8982	0.161	0.0214
	MVPA (MET-min/wk)	-0.0049	0.0088	0.570		-0.0052	0.0110	0.639	
	*Body Weight (kg)	-----	-----	-----		-0.9884	1.0026	0.326	
	*Age (years)	-----	-----	-----		0.9590454	1.5152	0.528	
	*Sex (female)	-----	-----	-----		-3.6907	40.4083	0.927	
	*Education (College degree or higher)	-----	-----	-----		14.4748	27.8643	0.605	
Reaction Time Difference Percent Change Score	Intercept	21.8957	2.1024	0.000	0.0025	30.6873	19.4311	0.117	0.0184
	MVPA (MET-min/wk)	-0.0006	0.0011	0.597		-0.0007	0.0014	0.613	
	*Body Weight (kg)	-----	-----	-----		-0.1215	0.1266	0.339	
	*Age (years)	-----	-----	-----		0.0288	0.1913	0.881	
	*Sex (female)	-----	-----	-----		-0.8754	5.1020	0.864	
	*Education (College degree or higher)	-----	-----	-----		2.4021	3.5182	0.496	

*Variable was forced in the model as covariate for the adjusted analysis

**Reaction Time Difference computed as two-back reaction time minus one-back reaction time

Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

Table 12 Association Between Moderate-to-Vigorous-Intensity Physical Activity and N-Back Accuracy Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
One-Back Accuracy	Intercept	0.8852	0.0267	0.000	0.0092	1.0198	0.2426	0.000	0.0583
	MVPA (MET-min/wk)	$1.44e^{-05}$	$1.42e^{-06}$	0.311		$2.17e^{-05}$	$1.74e^{-05}$	0.215	
	*Body Weight (kg)	-----	-----	-----		-0.0004	0.0016	0.814	
	*Age (years)	-----	-----	-----		-0.0038	0.0024	0.110	
	*Sex (female)	-----	-----	-----		0.0474	0.0637	0.458	
	*Education (College degree or higher)	-----	-----	-----		0.0385	0.0439	0.383	
Two-Back Accuracy	Intercept	0.8026	0.0302	0.000	.0011	1.0962	0.2737	0.000	0.0563
	MVPA (MET-min/wk)	$5.64e^{-06}$	$1.6e^{-05}$	0.726		$4.69e^{-06}$	$1.96e^{-05}$	0.811	
	*Body Weight (kg)	-----	-----	-----		-0.0012	0.0018	0.531	
	*Age (years)	-----	-----	-----		-0.0050	0.0027	0.065	
	*Sex (female)	-----	-----	-----		-0.0029	0.0719	0.968	
	*Education (College degree or higher)	-----	-----	-----		0.0554	0.0496	0.266	
##**Accuracy Difference Score	Intercept	-0.0826	0.0160	0.000	0.0095	0.1779	0.1514	0.242	0.0687
	MVPA (MET-min/wk)	$-8.78e^{-06}$	$8.51e^{-06}$	0.305		$-3.26e^{-05}$	$1.33e^{-05}$	0.016	
	*Body Weight (kg)	-----	-----	-----		-0.0013	0.0010	0.196	
	*Age (years)	-----	-----	-----		-.0014	0.0014	0.333	
	*Sex (female)	-----	-----	-----		-0.0886	0.0410	0.033	
	*Education (College degree or higher)	-----	-----	-----		0.0248	0.0266	0.354	
##Accuracy Difference Percent Change Score	Intercept	-7.226396	2.4528	0.004	0.0145	16.01	18.0931	0.378	0.0667
	MVPA (MET-min/wk)	-0.0017	0.0013	0.203		-0.0033	0.0016	0.038	
	*Body Weight (kg)	-----	-----	-----		-0.0891	0.1158	0.444	
	*Age (years)	-----	-----	-----		-0.2451	0.1737	0.161	
	*Sex (female)	-----	-----	-----		-8.145	4.7369	0.088	
	*Education (College degree or higher)	-----	-----	-----		3.7800	3.2527	0.248	

*Variable was forced in the model as covariate for the adjusted analysis

**Accuracy Difference computed as two-back accuracy minus one-back accuracy

#Variable was log-transformed in the model

##Influential points were removed from variable

Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

4.1.8 Associations Between Change in Light-Intensity Physical Activity and Change in Cognitive Outcomes

Analyses were conducted to assess the change in light-intensity physical activity volume and change in cognitive outcomes. The change in N-Back reaction time outcomes are shown in Table 13 while the N-Back accuracy outcomes are shown in Table 14.

No significant associations were seen in unadjusted or adjusted models between light-intensity physical activity and change in one-back or change in two-back reaction times (Table 13). However, there were significant associations observed for analyses involving light-intensity physical activity and both absolute and percent change in reaction time difference. In unadjusted models between change in reaction time difference and light-intensity physical activity, associations were not significant (p=0.410). However, in the adjusted analysis a negative association was observed (β=-0.0272, p=0.025). Similarly, the unadjusted model between change in reaction time percent change score did not present a significant association with light-intensity physical activity (p=0.410), but there was a significant association observed in the adjusted analysis (β=-0.0031, p=0.043). No covariates were significant in any of the adjusted models presented in Table 13.

There were no significant associations in unadjusted or adjusted models between light-intensity physical activity and change in one-back or two-back accuracy scores (Table 14). However, the unadjusted analyses with change in accuracy difference score showed a negative association with change in light-intensity physical activity (β=-4.77e^{-05}, p=0.014). After adjustment for covariates, the negative association remained significant (β=-05.51e^{-05}, p=0.005). A similar pattern was observed for the analysis of the percent change score. In the unadjusted

model, a negative association was found (β=-0.033, p=0.042), and this remained significant in the adjusted analysis (β=-0.0037, p=0.026). None of the covariates were significant in any of the adjusted models of Table 14.

Table 13 Association Between Change in Light-Intensity Physical Activity and Change in N-Back Reaction Time Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in One-Back Reaction Time	Intercept	-40.1726	17.6260	0.025	0.0025	38.7378	110.6994	0.727	0.0494
	Change in LPA (MET-min/wk)	0.0078	0.0149	0.601		0.0126	0.0151	0.406	
	*Change in Weight (kg)	-----	-----	-----		0.6467	2.1609	0.765	
	*Age (years)	-----	-----	-----		-1.8263	1.9853	0.360	
	*Sex (female)	-----	-----	-----		55.78979	40.8371	0.175	
	*Education (College degree or higher)	-----	-----	-----		-48.10846	36.9915	0.196	
Change in Two-Back Reaction Time	Intercept	-29.6989	16.4985	0.075	0.0040	132.8434	104.3488	0.206	0.0374
	Change in LPA (MET-min/wk)	-0.0093	0.0140	0.508		-0.0103	0.1426	0.470	
	*Change in Weight (kg)	-----	-----	-----		0.6528	2.0369	0.749	
	*Age (years)	-----	-----	-----		-2.004	1.8714	0.287	
	*Sex (female)	-----	-----	-----		-63.7684	38.4932	0.101	
	*Education (College degree or higher)	-----	-----	-----		-20.7310	34.8694	0.553	
##**Change in Reaction Time Difference Score	Intercept	10.4738	19.4607	0.592	0.0098	62.1633	79.4284	0.436	0.1293
	Change in LPA (MET-min/wk)	-0.0171	0.0165	0.301		-0.0272	0.0120	0.025	
	*Change in Weight (kg)	-----	-----	-----		1.1133	1.5294	0.468	
	*Age (years)	-----	-----	-----		0.2397	1.4240	0.867	
	*Sex (female)	-----	-----	-----		-89.9922	29.2449	0.003	
	*Education (College degree or higher)	-----	-----	-----		27.0280	40.2447	0.311	
##Change in Reaction Time Difference Percent Change Score	Intercept	-0.5688	2.0656	0.784	0.0064	10.624	9.9013	0.286	0.1277
	Change in LPA (MET-min/wk)	-0.0014	0.0017	0.410		-0.0031	0.0015	0.043	
	*Change in Weight (kg)	-----	-----	-----		0.1775	0.1907	0.354	
	*Age (years)	-----	-----	-----		-0.0117	0.1775	0.948	
	*Sex (female)	-----	-----	-----		-11.5850	3.6456	0.002	
	*Education (College degree or higher)	-----	-----	-----		3.3106	3.3114	0.320	

*Variable was forced in the model as covariate for the adjusted analysis

**Reaction Time Difference computed as two-back reaction time minus one-back reaction time

#Variable was log-transformed in the model

##Influential points were removed from variable

Note: LPA = Light-Intensity Physical Activity

Table 14 Association Between Change in Light-Intensity Physical Activity and Change in N-Back Accuracy Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in One-Back Accuracy	Intercept	-0.0271	0.03125	0.0387	0.0203	0.1695	0.1957	0.388	0.0716
	Change in LPA (MET-min/wk)	$3.98e^{-05}$	$2.65e^{-05}$	0.136		$4.89e^{-05}$	$2.67e^{-05}$	0.070	
	*Change in Weight (kg)	-----	-----	-----		0.0058	0.003	0.133	
	*Age (years)	-----	-----	-----		-0.0003	0.0035	0.936	
	*Sex (female)	-----	-----	-----		-0.0566	0.0722	0.434	
	*Education (College degree or higher)	-----	-----	-----		-0.1193	0.0654	0.071	
Change in Two-Back Accuracy	Intercept	0.0746	0.0663	0.263	0.0075	-0.2921	0.4248	0.493	0.0155
	Change in LPA (MET-min/wk)	$-5.11e^{-05}$	$5.62e^{-05}$	0.365		$-5.4e^{-05}$	$5.81e^{-05}$	0.354	
	*Change in Weight (kg)	-----	-----	-----		-0.0031	0.0083	0.705	
	*Age (years)	-----	-----	-----		0.0050	0.0076	0.515	
	*Sex (female)	-----	-----	-----		0.0758	0.1567	0.630	
	*Education (College degree or higher)	-----	-----	-----		0.0712	0.1420	0.617	
##**Change in Accuracy Difference Score	Intercept	0.0183	0.0225	0.418	0.0550	0.0575	0.1408	0.684	0.1089
	Change in LPA (MET-min/wk)	$-4.77e^{-05}$	$1.9e^{-05}$	0.014		$-5.51e^{-05}$	$1.92e^{-05}$	0.005	
	*Change in Weight (kg)	-----	-----	-----		-0.0047	0.0027	0.089	
	*Age (years)	-----	-----	-----		-0.0030	0.0025	0.244	
	*Sex (female)	-----	-----	-----		0.0112	0.0518	0.829	
	*Education (College degree or higher)	-----	-----	-----		0.0599	0.0469	0.205	
##Change in Accuracy Difference Percent Change Score	Intercept	3.6651	1.9269	0.060	0.0393	4.3343	12.2334	0.724	0.0641
	Change in LPA (MET-min/wk)	-0.0033	0.0016	0.042		-0.0037	0.0016	0.026	
	*Change in Weight (kg)	-----	-----	-----		-0.3270	0.2371	0.171	
	*Age (years)	-----	-----	-----		-0.1379	0.2187	0.530	
	*Sex (female)	-----	-----	-----		1.1357	4.5831	0.805	
	*Education (College degree or higher)	-----	-----	-----		2.2634	4.0592	0.578	

*Variable was forced in the model as covariate for the adjusted analysis
**Accuracy Difference computed as two-back accuracy minus one-back accuracy
#Variable was log-transformed in the model
##Influential points were removed from variable
Note: LPA = Light-Intensity Physical Activity

4.1.9 Associations Between Change in Moderate-to-Vigorous-Intensity Physical activity and Change in Cognitive Outcomes

As shown in Table 15, there were no significant associations between moderate-to-vigorous physical activity and change in reaction time outcomes in any of the unadjusted or adjusted models. A similar pattern was observed for the analyses of the association between the change in moderate-to-vigorous physical activity and change in accuracy outcomes (Table 16).

Table 15 Association Between Change in Moderate-to-Vigorous-Intensity Physical Activity and Change in N-Back Reaction Time Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in One-Back Reaction Time	Intercept	-24.7230	18.8357	0.192	0.0142	45.7833	110.7311	0.680	0.0479
	Change in MVPA (MET-min/wk)	-0.0157	0.0125	0.212		-0.0098	0.01354	0.469	
	*Change in Weight (kg)	-----	-----	-----		0.15802	2.183173	0.942	
	*Age (years)	-----	-----	-----		-1.6583	2.005	0.410	
	*Sex (female)	-----	-----	-----		46.0728	42.0939	0.276	
	*Education (College degree or higher)	-----	-----	-----		-46.6067	36.8949	0.209	
Change in Two-Back Reaction Time	Intercept	-23.6103	17.6661	0.184	0.0118	134.6296	103.4331	0.196	0.0533
	Change in MVPA (MET-min/wk)	-0.0133	0.0117	0.257		-0.0192	0.0127	0.133	
	*Change in Weight (kg)	-----	-----	-----		0.2731	2.0393	0.894	
	*Age (years)	-----	-----	-----		-1.5898	1.8733	0.398	
	*Sex (female)	-----	-----	-----		-76.7177	39.3196	0.054	
	*Education (College degree or higher)	-----	-----	-----		-26.73595	34.4632	0.440	
**Change in Reaction Time Difference Score	Intercept	1.1127	21.0202	0.958	0.0003	88.8463	121.2574	0.465	0.0703
	Change in MVPA (MET-min/wk)	0.0023	0.01392	0.868		-0.0093	0.0148	0.532	
	*Change in Weight (kg)	-----	-----	-----		0.1151	2.3907	0.962	
	*Age (years)	-----	-----	-----		0.0686	2.1961	0.975	
	*Sex (female)	-----	-----	-----		-122.7905	46.0954	0.009	
	*Education (College degree or higher)	-----	-----	-----		19.8707	40.4021	0.624	
Change in Reaction Time Difference Percent Change Score	Intercept	-1.3403	2.2221	0.548	0.0001	22.5669	12.7337	0.079	0.0827
	Change in MVPA (MET-min/wk)	0.0002	0.0015	0.911		-0.0008	0.0016	0.610	
	*Change in Weight (kg)	-----	-----	-----		0.2089	0.2506	0.407	
	*Age (years)	-----	-----	-----		-0.2075	0.2299	0.369	
	*Sex (female)	-----	-----	-----		-14.4588	4.9104	0.004	
	*Education (College degree or higher)	-----	-----	-----		-0.5648	4.2300	0.894	

*Variable was forced in the model as covariate for the adjusted analysis

**Reaction Time Difference computed as two-back reaction time minus one-back reaction time

Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

Table 16 Association Between Change in Moderate-to-Vigorous-Intensity Physical Activity and Change in N-Back Accuracy Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in One-Back Accuracy	Intercept	0.0126	0.0337	0.710	0.0151	0.1958	0.1968	0.322	0.0606
	Change in MVPA (MET-min/wk)	$-2.88e^{-05}$	$2.3e^{-05}$	0.199		$-3.47e^{-05}$	$2.4e^{-05}$	0.152	
	*Change in Weight (kg)	-----	-----	-----		0.0040	0.0039	0.305	
	*Age (years)	-----	-----	-----		0.0003	0.0036	0.933	
	*Sex (female)	-----	-----	-----		-0.0916	0.0748	0.223	
	*Education (College degree or higher)	-----	-----	-----		-0.1129	0.0656	0.088	
Change in Two-Back Accuracy	Intercept	0.0442	0.0715	0.538	0.0004	-0.3138	.4263	0.463	0.0079
	Change in MVPA (MET-min/wk)	$1.01e^{-05}$	$4.74e^{-05}$	0.831		$1.18e^{-05}$	$5.21e^{-05}$	0.822	
	*Change in Weight (kg)	-----	-----	-----		-0.0019	0.0084	0.819	
	*Age (years)	-----	-----	-----		0.0049	0.0077	0.529	
	*Sex (female)	-----	-----	-----		0.0941	0.1620	0.563	
	*Education (College degree or higher)	-----	-----	-----		0.0594	0.1420	0.677	
**Change in Accuracy Difference Score	Intercept	0.0316	0.0790	0.690	0.0050	-0.5096	0.4671	0.278	0.0282
	Change in MVPA (MET-min/wk)	$3.89e^{-05}$	$5.23e^{-05}$	0.459		$4.65e^{-05}$	$5.71e^{-05}$	0.418	
	*Change in Weight (kg)	-----	-----	-----		-0.0059	0.0092	0.522	
	*Age (years)	-----	-----	-----		0.0046	0.0085	0.590	
	*Sex (female)	-----	-----	-----		0.1857	0.1776	0.298	
	*Education (College degree or higher)	-----	-----	-----		0.1723	0.1556	0.271	
Change in Accuracy Difference Percent Change Score	Intercept	0.4668	2.7981	0.868	0.0061	14.4687	16.3965	0.380	0.0466
	Change in MVPA (MET-min/wk)	-0.0015	0.0019	0.418		-0.0018	0.0020	0.106	
	*Change in Weight (kg)	-----	-----	-----		-0.5263	0.3227	0.202	
	*Age (years)	-----	-----	-----		-0.3803	0.2960	0.202	
	*Sex (female)	-----	-----	-----		1.3154	6.3229	0.823	
	*Education (College degree or higher)	-----	-----	-----		-3.9002	5.4467	0.476	

*Variable was forced in the model as covariate for the adjusted analysis

**Accuracy Difference computed as two-back accuracy minus one-back accuracy

Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

4.1.10 Associations Between Light-Intensity and Moderate-to-Vigorous-Intensity Physical Activity and Volumetric Outcomes at Baseline

Table 17 represents the analyzes for associations between collapsed volumes of the basal ganglia and hippocampus within the brain. There were no significant associations found between volumes of light-intensity physical activity and volumes of these areas.

However, relationships emerged in consideration of moderate-to-vigorous physical activity, shown in Table 18. Unadjusted analyses showed a significant positive association between moderate-to-vigorous physical activity and collapsed nucleus accumbens volumes (β=0.0374, p=0.004). The association between moderate-to-vigorous physical activity and collapsed nucleus accumbens volumes remained significant in the adjusted analysis (β=0.0436, p=0.008). There were no significant associations in unadjusted or adjusted models between moderate-to-vigorous intensity physical activity and volume of the caudate nucleus.

In the unadjusted analyses, moderate-to-vigorous physical activity was significantly associated with the hippocampus (β=0.1714, p=0.002), pallidum (β=0.0697, p=0.004), and putamen (β=0.1819, p=0.005), only non-adjusted analyses were significant. However, moderate-to-vigorous physical was not significantly associated with these outcomes in the adjusted analyses.

Table 17 Association Between Light-Intensity Physical Activity and Volumetric Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Collapsed Accumbens Volume	Intercept	861.9542	43.9266	0.000	0.0164	857.8866	213.125	0.000	0.0357
	LPA (MET-min/wk)	0.0205	0.0151	0.176		0.0182	0.016	0.252	
	Body Weight (kg)	-----	-----	-----		0.7992	1.4445	0.581	
	*Age (years)	-----	-----	-----		-1.076	2.2376	0.632	
	*Sex (female)	-----	-----	-----		-38.3613	50.0358	0.445	
	*Education (College degree or higher)	-----	-----	-----		23.2804	41.7867	0.579	
Collapsed Caudate Volume	Intercept	6774.546	191.2454	0.000	0.0050	6728.234	903.9949	0.000	0.0741
	LPA (MET-min/wk)	-0.0489	0.0657	0.458		-0.0529	0.0669	0.431	
	Body Weight (kg)	-----	-----	-----		6.8511	6.1272	0.266	
	*Age (years)	-----	-----	-----		-13.3526	9.4912	0.162	
	*Sex (female)	-----	-----	-----		-176.4484	212.2327	0.408	
	*Education (College degree or higher)	-----	-----	-----		250.3828	177.2432	0.161	
Collapsed Hippocampus Volume	Intercept	7395.638	187.3788	0.000	0.0080	8273.46	899.8336	0.000	0.0473
	LPA (MET-min/wk)	0.0608	0.0644	0.347		0.0350	0.0666	0.600	
	Body Weight (kg)	-----	-----	-----		-0.8528	6.0990	0.889	
	*Age (years)	-----	-----	-----		-9.2578	9.4474	0.329	
	*Sex (female)	-----	-----	-----		-386.1902	211.2557	0.070	
	*Education (College degree or higher)	-----	-----	-----		-12.8662	176.4273	0.942	
Collapsed Pallidum Volume	Intercept	3374.963	81.4733	0.000	0.0103	3642.662	377.5918	0.000	0.1147
	LPA (MET-min/wk)	0.0301	0.0280	0.284		0.0136	0.0279	0.628	
	Body Weight (kg)	-----	-----	-----		0.3184	2.5593	0.901	
	*Age (years)	-----	-----	-----		-2.4451	3.9644	0.539	
	*Sex (female)	-----	-----	-----		-255.9923	88.6480	0.005	
	*Education (College degree or higher)	-----	-----	-----		80.2779	74.0331	0.281	

Table 17 (continued).

Collapsed Putamen Volume	Intercept	9291.099	215.8675	0.000	0.0233	10565.21	101.847	0.000	0.0992
	LPA (MET-min/wk)	0.1207	0.0742	0.107		0.1015	0.0752	0.180	
	Body Weight (kg)	-----	-----	-----		0.9011	6.8853	0.895	
	*Age (years)	-----	-----	-----		-22.9414	10.6655	0.034	
	*Sex (female)	-----	-----	-----		-431.1052	238.4925	0.073	
	*Education (College degree or higher)	-----	-----	-----		103.8677	199.1737	0.603	

*Variable was forced in the model as covariate for the adjusted analysis
Note: LPA = Light-Intensity Physical Activity

Table 18 Association Between Moderate-to-Vigorous Physical Activity and Volumetric Outcomes at Baseline

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Collapsed Accumbens Volume	Intercept	867.5796	24.1986	0.000	0.0711	651.9164	223.5231	0.004	0.0869
	MVPA (MET-min/wk)	0.0374	0.0128	0.004		0.0436	0.0160	0.008	
	Body Weight (kg)	-----	-----	-----		1.7972	1.4561	0.220	
	*Age (years)	-----	-----	-----		-0.1302	2.2005	0.953	
	*Sex (female)	-----	-----	-----		42.7545	58.6893	0.468	
	*Education (College degree or higher)	-----	-----	-----		23.8743	40.4704	0.556	
Collapsed Caudate Volume	Intercept	6533.254	107.6077	0.000	0.0197	6015.706	970.226	0.000	0.0819
	MVPA (MET-min/wk)	0.0852	0.0571	0.138		0.0862	0.0696	0.218	
	Body Weight (kg)	-----	-----	-----		9.0186	6.3206	0.157	
	*Age (years)	-----	-----	-----		-11.8126	9.5516	0.219	
	*Sex (female)	-----	-----	-----		45.6382	254.7474	0.858	
	*Education (College degree or higher)	-----	-----	-----		277.6383	175.6661	0.117	
[##]Collapsed Hippocampus Volume	Intercept	7332.959	102.1376	0.000	0.0828	8696.782	950.1287	0.000	0.0686
	MVPA (MET-min/wk)	0.1714	0.05417	0.002		0.0779	0.0796	0.330	
	Body Weight (kg)	-----	-----	-----		-5.6591	6.1668	0.361	
	*Age (years)	-----	-----	-----		-10.8383	8.8649	0.224	
	*Sex (female)	-----	-----	-----		-321.5267	245.0272	0.192	
	*Education (College degree or higher)	-----	-----	-----		-34.9159	950.1287	0.832	
Collapsed Pallidum Volume	Intercept	3363.897	44.71968	0.000	0.0721	3453.327	404.1215	0.000	0.1271
	MVPA (MET-min/wk)	0.0697	0.0237	0.004		0.0383	0.0290	0.189	
	Body Weight (kg)	-----	-----	-----		1.2011	2.6327	0.649	
	*Age (years)	-----	-----	-----		-1.6222	3.9784	0.684	
	*Sex (female)	-----	-----	-----		-183.0106	106.1082	0.087	
	*Education (College degree or higher)	-----	-----	-----		81.5055	73.169	0.268	

Table 18 (continued).

Collapsed Putamen Volume	Intercept	9373.795	119.4646	0.000	0.0691	10006.16	1086.202	0.000	0.1136
	MVPA (MET-min/wk)	0.1819	0.0634	0.005		0.1475	0.0779	0.061	
	Body Weight (kg)	-----	-----	-----		4.1994	7.0754	0.554	
	*Age (years)	-----	-----	-----		-19.592	10.6923	0.070	
	*Sex (female)	-----	-----	-----		-184.5374	285.1721	0.519	
	*Education (College degree or higher)	-----	-----	-----		94.1108	196.6461	0.633	

*Variable was forced in the model as covariate for the adjusted analysis
##Influential points were removed from variable
Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

4.1.11 Associations Between Change in Light-Intensity and Moderate-to-Vigorous-Intensity Physical Activity and Change in Volumetric Outcomes

Tables 19 presents the associations between change in light-intensity physical activity and change in volumes of the brain, post-intervention. As shown, there were no statistically significant associations in unadjusted or adjusted models between change in volume of light-intensity physical activity or change in volume of brain regions of the basal ganglia (including the nucleus accumbens, caudate nucleus, pallidum, and putamen) or the hippocampus. There is also a lack of statistically significant associations in consideration of moderate-to-vigorous physical activity (Table 20).

Table 19 represents the absolute change of light-intensity physical activity and volumetric outcomes. Additional exploratory analyses were conducted to examine the associations between percent change of these same variables (Table 24 and 25 in Appendix). These exploratory analyses found similar results, with no statistically significant associations in unadjusted or adjusted models between percent change in volumes of either light-intensity or moderate-to-vigorous physical activity and percent change in regional brain volumes.

Table 19 Association Between Change in Light-Intensity Physical Activity and Change in Volumetric Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in Collapsed Accumbens Volume	Intercept	-4.7395	14.9194	0.751	0.0050	-20.4014	93.1218	0.827	0.0635
	Change in LPA (MET-min/wk)	-0.0093	0.0126	0.462		-0.01478	0.0127	0.248	
	*Change in Weight (kg)	-----	-----	-----		-1.2947	1.8178	0.478	
	*Age (years)	-----	-----	-----		0.3738	1.6701	0.823	
	*Sex (female)	-----	-----	-----		-56.5872	34.3527	0.102	
	*Education (College degree or higher)	-----	-----	-----		44.3504	31.1177	0.157	
Change in Collapsed Caudate Volume	Intercept	-83.6919	51.9663	0.110	0.0039	-330.7607	332.7231	0.322	0.0135
	Change in LPA (MET-min/wk)	0.0288	0.0441	0.514		0.0260	0.0455	0.569	
	*Change in Weight (kg)	-----	-----	-----		-0.2701	6.4949	0.967	
	*Age (years)	-----	-----	-----		5.2464	5.9672	0.381	
	*Sex (female)	-----	-----	-----		-31.2022	122.7419	0.800	
	*Education (College degree or higher)	-----	-----	-----		42.94181	111.1834	0.700	
Change in Collapsed Hippocampus Volume	Intercept	-77.8598	54.0296	0.152	0.0140	-544.1783	341.3671	0.114	0.0491
	Change in LPA (MET-min/wk)	0.0570	0.0458	0.216		0.0521	0.0466	0.267	
	*Change in Weight (kg)	-----	-----	-----		2.919	6.6636	0.662	
	*Age (years)	-----	-----	-----		9.3031	6.1223	0.132	
	*Sex (female)	-----	-----	-----		-45.0319	125.9306	0.721	
	*Education (College degree or higher)	-----	-----	-----		151.42	114.0718	0.187	
Change in Collapsed Pallidum Volume	Intercept	-57.6543	23.1801	0.014	0.0204	-211.278	145.2557	0.149	0.0707
	Change in LPA (MET-min/wk)	0.0296	0.0197	0.134		0.0246	0.0198	0.217	
	*Change in Weight (kg)	-----	-----	-----		-5.6707	2.8355	0.048	
	*Age (years)	-----	-----	-----		2.31965	2.6051	0.375	
	*Sex (female)	-----	-----	-----		-1.4474	53.5849	0.979	
	*Education (College degree or higher)	-----	-----	-----		-0.7344	48.5389	0.880	

Table 19 (continued).

Change in Collapsed Putamen Volume	Intercept	-63.8596	55.2314	0.250	0.0003	-130.6067	344.6581	0.705	0.0595
	Change in LPA (MET-min/wk)	-0.0082	0.0468	0.862		-.0246	0.04710	0.603	
	*Change in Weight (kg)	-----	-----	-----		-2.1589	6.7279	0.749	
	*Age (years)	-----	-----	-----		3.8504	6.1813	0.535	
	*Sex (female)	-----	-----	-----		-257.1726	127.1447	0.046	
	*Education (College degree or higher)	-----	-----	-----		106.0663	115.1716	0.359	

*Variable was forced in the model as covariate for the adjusted analysis
Note: LPA = Light-Intensity Physical Activity

Table 20 Association Between Change in Moderate-to-Vigorous Intensity Physical Activity and Change in Volumetric Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
Change in Collapsed Accumbens Volume	Intercept	-19.4940	15.9521	0.224	0.0156	-27.8362	93.4182	0.766	0.0565
	Change in MVPA (MET-min/wk)	0.01388	0.0106	0.192		0.0086	0.0114	0.453	
	*Change in Weight (kg)	-----	-----	-----		-0.8065	1.8418	0.662	
	*Age (years)	-----	-----	-----		0.2363	1.6919	0.889	
	*Sex (female)	-----	-----	-----		-47.4566	35.5125	0.184	
	*Education (College degree or higher)	-----	-----	-----		42.0815	31.1263	0.179	
Change in Collapsed Caudate Volume	Intercept	-79.2702	55.9494	0.159	0.0008	-322.2247	333.0675	0.336	0.0104
	Change in MVPA (MET-min/wk)	0.0109	0.0371	0.769		0.0012	0.040739	0.977	
	*Change in Weight (kg)	-----	-----	-----		-0.6606	6.567	0.920	
	*Age (years)	-----	-----	-----		5.1573	6.0322	0.395	
	*Sex (female)	-----	-----	-----		-34.6142	126.614	0.785	
	*Education (College degree or higher)	-----	-----	-----		49.7919	110.9758	0.655	
Change in Collapsed Hippocampus Volume	Intercept	-47.6513	58.4832	0.417	0.0003	-521.0655	342.8718	0.132	0.0397
	Change in MVPA (MET-min/wk)	-0.0065	0.0387	0.867		-0.0192	0.0419	0.648	
	*Change in Weight (kg)	-----	-----	-----		1.5179	6.7601	0.823	
	*Age (years)	-----	-----	-----		9.5616	6.2098	0.127	
	*Sex (female)	-----	-----	-----		-68.6512	130.3411	0.600	
	*Education (College degree or higher)	-----	-----	-----		161.3753	114.2425	0.161	
Changed in Collapsed Pallidum Volume	Intercept	-56.7711	25.0698	0.026	0.0085	-203.9455	146.2088	0.166	0.0575
	Change in MVPA (MET-min/wk)	0.0160	0.0166	0.337		0.0039	0.0179	0.829	
	*Change in Weight (kg)	-----	-----	-----		-5.9624	2.8827	0.041	
	*Age (years)	-----	-----	-----		2.1795	2.6480	0.412	
	*Sex (female)	-----	-----	-----		-2.6714	55.5806	0.962	
	*Education (College degree or higher)	-----	-----	-----		-0.3679	48.7158	0.994	

Table 20 (continued).

Change in Collapsed Putamen Volume	Intercept	-110.0598	58.8323	0.064	0.0184	-147.2576	344.1118	0.670	0.0615
	Change in MVPA (MET-min/wk)	0.0557	0.0390	0.156		0.0297	0.04209	0.481	
	*Change in Body Weight (kg)	-----	-----	-----		-0.9048	6.7845	0.894	
	*Age (years)	-----	-----	-----		3.3092	6.2322	0.597	
	*Sex (female)	-----	-----	-----		-230.1386	130.8125	0.081	
	*Education (College degree or higher)	-----	-----	-----		104.9953	114.6557	0.362	

*Variable was forced in the model as covariate for the adjusted analysis
Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

4.1.12 Association Between Cognitive and Volumetric Outcomes

Table 21 outlines the associations between cognitive and volumetric outcomes at baseline. Regarding the N-back response time outcomes, significant associations exist between one-back response time and collapsed volumes of the nucleus accumbens (p=0.0242), caudate nucleus (p=0.0431), and hippocampus (p=0.0083). There were no statistically significant associations between two-back response time and volumetric outcomes. Statistically significant relationships were found between response time difference and collapsed volumes of the pallidum (p=0.0100) and hippocampus (p=0.0035). Lastly, response time percent difference was significantly associated with collapsed volumes of the caudate nucleus (p=0.0285), pallidum (p=0.0042), and hippocampus (p=0.0014).

N-back accuracy outcomes were associated with the collapsed volume of less areas of the brain. One-back and two-back accuracy was significantly associated with collapsed volume of the hippocampus (p=0.0189 and p=0.0336, respectively). Accuracy difference and percent difference were not significantly associated with collapses volume of the brain.

Table 22 highlights the associations between cognitive and volumetric outcomes measured at 12-months. One-back response time was associated with collapsed volumes of the nucleus accumbens (p=0.0008), pallidum (p=0.0392), putamen (p=0.0381), and hippocampus (p=0.0412). Therefore, the only region of the brain not associated with one-back response time was the caudate nucleus. Two-back response time was associated with collapsed volume of the nucleus accumbens (p=0.0341). No statistically significant associations were found between response time difference and any volumetric variable. However, one statistically significant association was found with response time percent difference, which was with collapsed volume of the hippocampus

(p=0.0014). One-back accuracy was associated with collapsed volumes of the nucleus accumbens (p=0.0016) and caudate nucleus (p=0.0473). Two-back accuracy was associated with two-back accuracy (p=0.0451). Both absolute and percent difference in accuracy were associated with collapsed hippocampal volume (p=0.0089, p=0.0115, respectively.

Table 21 Spearman's Correlation Matrix between Cognitive and Volumetric Outcomes at Baseline

	One-Back Response Time	**Two-Back Response Time**	**One-Back and Two-Back Response Time Difference**	**One-Back and Two-Back Response Time Percent Difference**	**One-Back Accuracy**	**Two-Back Accuracy**	**Accuracy Difference**	**Accuracy Percent Difference**
Collapsed Accumbens Volume	-0.2101 (**p = 0.0242**)	-0.1293 (p = 0.1683)	0.0735 (p = 0.4353)	0.1069 (p = 0.2557)	0.0908 (p = 0.3345)	0.1482 (p = 0.1139)	0.0711 (p = 0.4502)	0.0878 (p = 0.3509)
Collapsed Caudate Volume	-0.1890 (**p = 0.0431**)	-0.0645 (p = 0.4936)	0.01714 (p = 0.0671)	0.2043 (**p = 0.0285**)	0.0569 (p = 0.5460)	0.0815 (p = 0.3866)	0.0631 (p = 0.5209)	0.0667 (p = 0.4785)
Collapsed Pallidum Volume	-0.1554 (p = 0.0972)	0.0085 (p = 0.9283)	0.2393 (**p = 0.0100**)	0.2648 (**p = 0.0042**)	0.0266 (p = 0.7776)	-0.0328 (p = 0.7276)	-0.1170 (p = 0.2130)	-0.1271 (p = 0.1760)
Collapsed Putamen Volume	-0.1391 (p = 0.1382)	-0.0726 (p = 0.4404)	0.0990 (p = 0.2923)	0.1319 (p = 0.1600)	0.0526 (p = 0.5767)	0.0360 (p = 0.7023)	-0.0772 (p = 0.4123)	-0.0759 (p = 0.4203)
Collapsed Hippocampus Volume	-0.2452 (**p = 0.0083**)	-0.0759 (p = 0.4204)	0.2701 (**p = 0.0035**)	0.2946 (**p = 0.0014**)	0.2186 (**p = 0.0189**)	0.1984 (**p = 0.0336**)	-0.0274 (p = 0.7716)	-0.0246 (p = 0.7940)

Note: Bolded p-values indicate a p-value < 0.05

Table 22 Spearman's Correlation Matrix between Cognitive and Volumetric Outcomes at 12-Months

	One-Back Response Time	Two-Back Response Time	One-Back and Two-Back Response Time Difference	One-Back and Two-Back Response Time Percent Difference	One-Back Accuracy	Two-Back Accuracy	Accuracy Difference	Accuracy Percent Difference
Collapsed Accumbens Volume	-0.3084 (**p = 0.0008**)	-0.1978 (**p = 0.0341**)	0.1137 (p = 0.2263)	0.1482 (p = 0.1173)	0.2913 (**p = 0.0016**)	0.1872 (**p = 0.0451**)	-0.0117 (p = 0.9008)	0.0071 (p = 0.9409)
Collapsed Caudate Volume	-0.1753 (p = 0.0609)	-0.1494 (p = 0.1109)	0.0271 (p = 0.7736)	0.0362 (p = 0.7031)	0.1854 (**p = 0.0473**)	0.1565 (p = 0.0949)	0.1111 (p = 0.2371)	0.1041 (p = 0.2727)
Collapsed Pallidum Volume	-0.1926 (**p = 0.0392**)	-0.0991 (p = 0.2922)	0.0851 (p = 0.3569)	0.1089 (p = 0.2510)	0.1331 (p = 0.1562)	0.1079 (p = 0.2512)	-0.0115 (p = 0.9028)	-0.0381 (p = 0.6890)
Collapsed Putamen Volume	-0.1936 (**p = 0.0381**)	-0.1503 (p = 0.1090)	0.0365 (p = 0.6985)	0.0654 (p = 0.4912)	0.1722 (p = 0.0657)	0.0397 (p = 0.6738)	-0.0560 (p = 0.5526)	-0.0657 (p = 0.4891)
Collapsed Hippocampus Volume	-0.1907 (**p = 0.0412**)	-0.1332 (p = 0.1558)	0.0239 (p = 0.7996)	0.0860 (**p = 0.0014**)	0.1794 (p = 0.3650)	0.2429 (p = 0.0550)	0.2349 (**p = 0.0089**)	0.2430 (**p = 0.0115**)

Note: Bolded p-values indicate a p-value < 0.05

5.0 Discussion

The purpose of this study was to examine the influence of body weight and physical activity, within the context of a behavioral weight loss intervention for adults with overweight or obesity, on selective measures of cognition and brain structure.

5.1 Brain Structure

One of the aims of this study was to examine the associations between body weight and brain structure, specifically, subcortical structures including the hippocampus and basal ganglia. It was hypothesized that higher body weight would be associated with smaller brain volumes at baseline prior to weight loss. However, these results do not support the proposed hypothesis of an association between these brain structures and body weight.

Obesity has been related to altered structure within the brain, independent of comorbid chronic conditions.[20,21] While the hippocampus has been more readily studied in the obesity literature, both the basal ganglia and hippocampal regions of the brain have been linked to obesity.[12,14,82] Other areas of the brain that have been associated with obesity and elevated BMI include the prefrontal cortex, occipital cortex, thalamus, among others.[13,14] Therefore, it may be possible that the current analysis did not capture associations within the basal ganglia or hippocampus, although they may occur in other regions of the brain. In addition, as this study included individuals within a specific BMI range, it may be possible that some effects are only observed at certain levels of obesity.[108]

In consideration of change across the intervention, it was hypothesized that reduced body weight would be associated with an increase in brain volume. While the associations between change in body weight and change in collapsed volume across the areas of the basal ganglia were all negative, as hypothesized, a significant association was only observed between the change in the pallidum and change in body weight. Moreover, there was a nonsignificant association between the change in hippocampal volume and change in body weight. This inconsistent direction in associations is aligned with the literature, as findings between brain structure and weight loss have been mixed. For example, studies have shown reduced, improved, or unchanged gray matter volumes following weight loss interventions.[104,105,106] Nonconsistency in findings may be due to the spread of intervention lengths within the literature. Change in gray matter volume has been seen in studies ranging from as little as six weeks to longitudinal studies studying effects for years.[104,105,106,150] This may suggest that there is an optimal window of time where the largest impact on gray matter volume is seen. Assessments of the current study were only performed at baseline and 12-months, which is a wide spread of time. Throughout this time, specifically for individuals randomized to the physical activity groups, there was a progressive ramp in physical activity volume, which may have influenced brain structure acutely. In addition, adherence and weight loss maintenance are current challenges within weight loss interventions, which may have begun to show around the 12-month assessment mark.

While this area of the literature is quite mixed with results showing increased, decreased, and unchanged brain volumes, it should be noted that the nonreduction of gray matter volume, seen in this study, may in fact be a valuable finding. While weight loss was not associated with a change in gray matter volume within most regions of the brain in this study, weight loss was not harmful and did not contribute to a reduction in volume. It is hypothesized that this may be due to

the addition of physical activity in this intervention. Reasons supporting this come from weight loss literature as reductions in gray matter volume has been seen following dietary interventions, that do not employ physical activity.[106]

In addition, this study aimed to evaluate the associations between physical activity and brain structure. At baseline, it was suggested that a negative association would exist between lower physical activity levels and smaller brain volumes, yet no significant associations were found. However, significant unadjusted outcomes were seen between volumes of moderate-to-vigorous physical activity and all measured regions of the brain, except the caudate nucleus. This study also hypothesized that there would be a positive association between the magnitude of increase in physical activity and the magnitude of increase in volume of the specific brain structures. No associations between change in light-intensity or change in moderate-to-vigorous intensity physical activity were seen with change in volumetric outcomes.

The results of this study are not consistent with the literature that has linked higher levels of physical activity to larger gray matter volumes within the brain.[38,118] Studies have shown that greater amounts of aerobic physical activity have been associated with greater gray matter volumes. This has been seen in the frontal cortex, parietal cortex, and temporal cortex of the brain.[37,38,122] One of the most readily studied areas of the brain shown to be responsive to exercise interventions includes the hippocampus. One explanation for the inconsistency between this study and the literature may be that physical activity may influence areas of the brain differently, explaining a potential variation in findings among regions of gray matter.[120,121] Thus, it may be important to examine other areas of the brain when assessing the influence that physical activity may have on brain structure and function. In addition, other cross-sectional studies have found that associations between regions of the brain may be dependent upon factors such as age, BMI, stress levels, sleep, and others.[87,123,124] Therefore, it is possible that other covariates should be considered for inclusion in future analyses.

5.2 Cognition

An aim of this study was to analyze the relationships between body weight and aspects of cognitive function. It was hypothesized that there would be an inverse association between body weight and cognitive variables at baseline. Obesity has been associated with poor cognitive function across a variety of domains, including executive function.[11,19,79,93,94] The results of this study demonstrated negative associations between body weight and both reaction time and accuracy outcomes at baseline; however, these associations in this study were not statistically significant.

When considering the change across the intervention, it was hypothesized that the magnitude of reduced body weight would be related to the magnitude of more favorable cognitive outcomes. Associations between change in body weight and change in reaction time and accuracy outcomes were not statistically significant. The literature in this area has been largely inconsistent as the contribution of weight loss interventions to improved cognitive function has been unclear. This mixed literature may be due to variety in aspects of weight loss interventions. For example, different modes of weight loss may influence cognitive function through different pathways, as outlined in Section 2.6.4. Surgical, dietary, and physical activity interventions have demonstrated associations with improved executive function previously.[30, 108] In addition, weight loss interventions within the literature have varied in duration. It is possible that conducting assessments at baseline and 12-months did not capture the changes in cognitive function that may have occurred earlier in the study. As short-term weight loss typically occurs within the first six months of an intervention, it is possible that cognitive benefits may be acutely seen during this window. Therefore, our findings align with prior studies that did not see relationships between weight loss and changes in cognitive function.[30,150]

Another aim of this study was to assess the associations between physical activity and cognitive function. Hypotheses proposed that there would be a negative association at baseline, where lower physical activity levels would be related to less favorable cognitive outcomes. At baseline, there were no statistically significant associations between light-intensity or moderate-to-vigorous physical activity volumes and reaction time outcomes. A statistically significant association was found between light-intensity physical activity and percent change in accuracy difference at baseline. Similarly, moderate-to-vigorous physical activity was associated with both the absolute and percent change in accuracy difference.

Following the intervention, it was suggested that the magnitude of increase in levels of physical activity would be related to the magnitude of increase in cognitive outcomes. Negative associations were found between light-intensity physical activity and absolute and percent change in reaction time and accuracy difference. There were no statistically significant associations between change in moderate-to-vigorous physical activity volumes and change in reaction time or accuracy outcomes.

Compared to the literature, in general, physical activity has been shown to influence a variety of cognitive domains.[121] This has been seen acutely in specific domains, such as executive function. Executive function has been largely and consistently shown to be influenced by physical activity. It has been suggested that this domain is sensitive to physical activity interventions.[128] However, the current study does not align with the current literature in this way. The N-Back test assess working memory, which is a domain of executive function, however, it is possible that the N-back test did not capture the other subdomains of executive function that may have been influenced by this intervention. Future studies should incorporate a broader cognitive battery to provide a larger picture of the influence of physical activity on cognition, especially given the inconsistency and mixed results within this body of literature. This is especially important for physical activity interventions as parameters of the intervention may contribute differently to individual domains of cognition.

It is also possible that important covariates, such as sleep, were contributing to the relationships tested within this study. As discussed in Section 2.7.4, sleep efficiency has been shown to mediate the relationship between physical activity and working memory.[145] Therefore, future analyses should take additional factors, such as sleep, into consideration.

5.3 Limitations, Strengths, and Future Directions

There are limitations that should be considered when interpreting the findings of the current study. In addition, these limitations should be factored into future research to continue bettering the understanding of the links between obesity, weight loss, physical activity, and the brain. These include the following:

1. Limitation: This study included 115 participants who self-selected to participate from the 383 participants enrolled in the parent study. Moreover, the majority of participants were white/Caucasian women. This sub-sample that was recruited by self-selection may have influenced the findings from this study of cognition and brain health.
    a. Future Direction: Future studies should *a-priori* recruit participants into a study of brain health that is of an appropriate sample size, with adequate representation by sex, race, and ethnicity to examine the association between obesity, weight loss, and physical activity on cognition and brain health.
2. Limitation: The eligibility criteria for the parent study include an age range of 18 to 55 years. Thus, given the existing literature to support that aging may negatively impact both cognition and brain structure, the eligibility age range for the parent study may have contributed to the lack of some of the hypothesized findings.
    a. Future Direction: Future studies should expand the age range to better determine the potential influence of the aging process on cognition and brain structure within the context of obesity and weight loss.

3. The eligibility criterion for the parent study was limited to adults with overweight or obesity (BMI of 25.0 to <40.0 kg/m^2) However, individuals with severe obesity (BMI ≥40 kg/m^2) were not eligible for the parent study, which may have influenced the findings.
    a. Future Direction: Future studies should expand the BMI range, and potentially consider body composition rather than BMI, to better determine the potential influence of the adiposity on cognition and brain structure within the context of obesity and weight loss. As described in Section 2.5.4, metabolically active adipose tissue may be involved in the mechanisms relating obesity to brain health.
4. Limitation: Aside from having overweight or obesity, and not being sufficiently physically active, the participants in this study were otherwise healthy with no known cardiovascular or other underlying metabolic disease. However, given that obesity has been associated with chronic conditions such as CVD, CHD, metabolic syndrome, type II diabetes, among others, in addition to risk factors of such, [4, 25] this may have limited the generalizability of the current findings.
    a. Future Direction: Following studies may consider expanding study criteria to include individuals with risk factors or diagnosis of chronic disease, in addition to obesity. This future work may provide a better understanding of the mechanisms in which obesity, which includes related chronic conditions, and brain health are related.

5. Limitation: Much like a majority of the related literature, this study was cross-sectional and observational in nature.[29] Neither the study design nor the analyses of this study appropriately target causality or mechanisms in which the variables in question are related.
    a. Future Direction: While the associations studied in this analysis begin to establish a potential relationship, or lack of association, between either weight or physical activity and either cognition or brain health, further research appears to be needed. The mechanisms in which physical activity and weight loss contribute to a change in brain health in humans are not fully understood.[41,42] Thus, experimental studies, which may include randomized trials, should be designed to better examine causality of any observed relationships and to examine the pathways in which variables may be related.
6. Limitation: This study included adults with overweight or obesity who also engaged in low levels of physical activity prior to undertaking the intervention. This narrow range of physical activity at baseline may have influenced the findings of this study, with this particularly influencing the cross-sectional analyses conducted on the baseline data.
    a. Future Direction: Future studies may need to study these questions in adults with overweight or obesity across a broader range of physical activity, particularly for cross-sectional data analysis.

Despite these potential limitations, this study also included strengths that should be highlighted. These strengths include the following:

1. This study included objective assessment of physical activity using a wearable device.
2. This study included measures of neuroimaging of the brain using MRI. Neuroimaging has promoted the noninvasive measurement of brain structure, with advanced technology promoting volumetric assessment of specific regions of the brain, such as the basal ganglia or hippocampus.[42]
3. The use of accelerometry in this study allowed for the differentiation between intensity of physical activity to be incorporated into the analyses. This study is novel in that it investigates the relationship between varying intensities of physical activity, which included both light-intensity and moderate-to-vigorous intensity, and aspects of brain health such as gray matter volume. This is a need for neurocognition literature as there is heterogeneity that exists among physical activity prescriptions used to intervene on aspects of brain health. It is suggested that parameters of physical activity may influence the brain through different avenues, therefore, there should be a high level of detail when reporting methods of analyses and interventions in the literature.

This study included recommended approaches to weight loss, including dietary, physical activity, and behavioral components.[4, 25, 53] The inclusion of midlife adults may be considered as a strength of the current study, as the existing literature base is heavily saturated with children and older adults. Therefore, this study will contribute to a better understanding of how obesity, weight loss, physical activity, and aspects of brain health are related across the lifespan.[33,43]

5.4 Conclusion

The current weight loss literature has been inconsistent, with many of the current studies in this area employing dietary and surgical intervention approaches. The current study provides results from a standard behavioral weight loss intervention, applying the recommended dietary, physical activity, and behavioral techniques. This provided the opportunity to examine the measures of cognition and brain structure with both weight and physical activity prior to and following a 12-month weight loss intervention in adults with obesity. The methods of this study also allowed for the separate analysis of both light-intensity and moderate-to-vigorous intensity physical activity and their association with selective cognitive and brain health outcomes.

While this study showed that there were reductions in body weight, increases in both light-intensity and moderate-to-vigorous physical activity, and improvements in measures of cognition, there was not observed change in volume measure of the brain. Moreover, this study, which was a secondary analysis of data from a randomized clinical trial, showed limited associations between either body weight or physical activity and either the cognitive outcomes or volume measures of the brain. Thus, within the context of a behavioral weight loss intervention, weight loss and physical activity may have limited impact on cognition and brain volume in middle-aged adults with overweight or obesity without other significant health concerns. However, these results should be interpreted with caution given the cross-sectional and observational nature of this study, which limited the ability of these data to support or not support causality. Thus, additional research may be needed to further elucidate the potential linkage between obesity and physical activity in this population group.

Appendix

Table 23 Association Between Percent Change in Body Weight and Percent Change in Volumetric Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
% Change in Collapsed Accumbens Volume	Intercept	-2.7745	0.2793	0.000	0.0004	0.0068	0.1123	0.952	0.0513
	% Change in Weight (kg)	0.2825	2.0050	0.888		-0.1652	0.2171	0.448	
	*Age (years)	-----	-----	-----		$-4.85e^{-5}$	0.0020	0.981	
	*Sex (female)	-----	-----	-----		-0.0740	0.0414	0.076	
	*Education (College degree or higher)	-----	-----	-----		0.0401	0.0381	0.294	
% Change in Collapsed Caudate Volume	Intercept	-0.0100	0.0127	0.428	0.0014	-0.0277	0.0509	0.587	0.0049
	% Change in Weight (kg)	-0.0368	0.0946	0.698		-0.0244	0.0984	0.805	
	*Age (years)	-----	-----	-----		0.0004	0.0009	0.677	
	*Sex (female)	-----	-----	-----		-0.0048	0.0188	0.797	
	*Education (College degree or higher)	-----	-----	-----		0.0071	0.0173	0.683	
% Change in Collapsed Hippocampus	Intercept	-0.0048	0.0128	0.710	0.0005	-0.0287	0.0510	0.575	0.0179
	% Change in Weight (kg)	-0.0226	0.0954	0.813		-0.0022	0.0986	0.982	
	*Age (years)	-----	-----	-----		0.0004	0.0009	0.675	
	*Sex (female)	-----	-----	-----		-0.0093	0.0188	0.622	
	*Education (College degree or higher)	-----	-----	-----		0.0215	0.0173	0.217	
% Change in Collapsed Pallidum	Intercept	-0.0267	0.0107	0.014	0.0412	-0.0352	0.0431	0.416	0.0427
	% Change in Weight (kg)	-0.1756	0.0801	0.030		-0.1691	0.0834	0.045	
	*Age (years)	-----	-----	-----		0.0003	0.0008	0.737	
	*Sex (female)	-----	-----	-----		-0.0028	0.0159	0.863	
	*Education (College degree or higher)	-----	-----	-----		-0.0009	0.0146	0.950	

Table 23 (continued).

% Change in Collapsed Putamen	Intercept	-0.0087	0.0099	0.383	0.0019	0.0070	0.0390	0.858	0.0436
	% Change in Weight (kg)	-0.0344	0.0739	0.642		-0.0038	0.0753	0.959	
	*Age (years)	-----	-----	-----		$1.35e^{-5}$	0.0007	0.985	
	*Sex (female)	-----	-----	-----		-0.0277	0.0144	0.056	
	*Education (College degree or higher)	-----	-----	-----		0.0119	0.0132	0.369	

*Variable was forced in the model as covariate for the adjusted analysis
#Variable was log-transformed in the model
##Influential points were removed from variable

Table 24 Association Between Percent Change in Light-Intensity Physical Activity and Percent Change in Volumetric Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
% Change in Collapsed Accumbens Volume	Intercept	0.0078	0.0191	0.685	0.0109	-0.0343	0.1118	0.760	0.0729
	% Change in LPA (MET-min/wk)	-0.0356	0.0324	0.275		-0.0501	0.0331	0.133	
	*% Change in Weight (kg)	-----	-----	-----		-0.19996	0.2162	0.358	
	*Age (years)	-----	-----	-----		0.0007	0.0020	0.733	
	*Sex (female)	-----	-----	-----		-0.0643	0.0384	0.118	
	*Education (College degree or higher)	-----	-----	-----		0.0588	0.1118	0.129	
% Change in Collapsed Caudate Volume	Intercept	-0.0076	0.0082	0.358	0.0006	-0.0489	0.0494	0.324	0.0148
	% Change in LPA (MET-min/wk)	-0.0036	0.0140	0.796		-0.0059	0.0146	0.688	
	*% Change in Weight (kg)	-----	-----	-----		-0.03556	0.0956	0.711	
	*Age (years)	-----	-----	-----		0.0008	0.0009	0.349	
	*Sex (female)	-----	-----	-----		-0.0064	0.01806	0.725	
	*Education (College degree or higher)	-----	-----	-----		0.0061	0.0170	0.720	
% Change in Collapsed Hippocampus Volume	Intercept	-0.0067	0.0077	0.384	0.0024	-0.0647	0.0456	0.159	0.0378
	% Change in LPA (MET-min/wk)	0.0066	0.0130	0.613		0.0029	0.0135	0.833	
	*% Change in Weight (kg)	-----	-----	-----		-0.0011	0.0882	0.990	
	*Age (years)	-----	-----	-----		0.0011	0.0008	0.166	
	*Sex (female)	-----	-----	-----		-0.0105	0.0167	0.529	
	*Education (College degree or higher)	-----	-----	-----		0.0197	0.0156	0.211	

Table 24 (continued).

% Change in Collapsed Pallidum Volume	Intercept	-0.0127	0.0071	0.077	0.0041	-0.429	0.0419	0.307	0.0611
	% Change in LPA (MET-min/wk)	0.0081	0.0121	0.504		0.0045	0.0124	0.719	
	*% Change in Weight (kg)	-----	-----	-----		-0.1731	0.0809	0.035	
	*Age (years)	-----	-----	-----		0.0005	0.0008	0.544	
	*Sex (female)	-----	-----	-----		-0.0062	0.01529	0.687	
	*Education (College degree or higher)	-----	-----	-----		-0.0056	0.0144	0.698	
% Change in Collapsed Putamen Volume	Intercept	-0.0040	0.0063	0.525	0.0048	-0.0184	0.0367	0.617	0.0673
	% Change in LPA (MET-min/wk)	-0.0077	0.0106	0.469		-0.0104	0.0108	0.338	
	*% Change in Weight (kg)	-----	-----	-----		-0.0146	0.0709	0.837	
	*Age (years)	-----	-----	-----		0.0005	0.0007	0.421	
	*Sex (female)	-----	-----	-----		-0.0273	0.0134	0.044	
	*Education (College degree or higher)	-----	-----	-----		0.0140	0.0126	0.269	

*Variable was forced in the model as covariate for the adjusted analysis.
Note: LPA = Light-Intensity Physical Activity

Table 25 Association Between Percent Change in Moderate-to-Vigorous Intensity Physical Activity and Percent Change in Volumetric Outcomes Post-Intervention

		Unadjusted Analysis				Adjusted Analysis			
Dependent Variable	**Variable**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**	**Beta**	**M.S.E.**	**p-value**	**Model R^2**
% Change in Collapsed Accumbens Volume	Intercept	$1.67e^{-5}$	0.0176	0.999	0.0016	-0.0290	0.1130	0.798	0.0551
	% Change in MVPA (MET-min/wk)	-0.0012	0.0029	0.678		-0.0015	0.0029	0.604	
	*% Change in Weight (kg)	-----	-----	-----		-0.1584	0.2165	0.466	
	*Age (years)	-----	-----	-----		0.0006	0.0021	0.766	
	*Sex (female)	-----	-----	-----		-0.0661	0.0413	0.112	
	*Education (College degree or higher)	-----	-----	-----		0.0493	0.0382	0.119	
% Change in Collapsed Caudate Volume	Intercept	-0.0092	0.0076	0.228	0.0007	-0.0472	0.0495	0.343	0.0136
	% Change in MVPA (MET-min/wk)	0.0003	0.0012	0.782		0.0003	0.0013	0.843	
	*% Change in Weight (kg)	-----	-----	-----		-0.0268	0.0949	0.771	
	*Age (years)	-----	-----	-----		0.0008	0.0009	0.365	
	*Sex (female)	-----	-----	-----		-0.0071	0.0181	0.696	
	*Education (College degree or higher)	-----	-----	-----		0.0045	0.0167	0.789	
% Change in Collapsed Hippocampus Volume	Intercept	-0.0057	0.0071	0.421	0.0016	-0.0644	0.0456	0.161	0.0380
	% Change in MVPA (MET-min/wk)	0.0005	0.0012	0.678		0.0003	0.0012	0.787	
	*% Change in Weight (kg)	-----	-----	-----		-0.0018	0.0875	0.983	
	*Age (years)	-----	-----	-----		0.0012	0.0008	0.167	
	*Sex (female)	-----	-----	-----		-0.0107	0.0167	0.523	
	*Education (College degree or higher)	-----	-----	-----		0.0199	0.0154	0.199	

Table 25 (continued).

% Changed in Collapsed Pallidum Volume	Intercept	-0.0119	0.0065	0.072	0.0054	-0.0421	0.0418	0.317	0.0631
	% Change in MVPA (MET-min/wk)	0.0008	0.0011	0.443		0.0006	0.0011	0.557	
	*% Change in Weight (kg)	-----	-----	-----		-0.1732	0.0802	0.033	
	*Age (years)	-----	-----	-----		0.0005	0.0008	0.555	
	*Sex (female)	-----	-----	-----		-0.0066	0.0141	0.668	
	*Education (College degree or higher)	-----	-----	-----		-0.0053	0.0418	0.707	
% Change in Collapsed Putamen Volume	Intercept	-0.0066	0.0058	0.253	0.0009	-0.0157	0.0368	0.671	0.0599
	% Change in MVPA (MET-min/wk)	0.0003	0.0009	0.756		0.0003	0.0009	0.756	
	*% Change in Weight (kg)	-----	-----	-----		-0.0018	0.0706	0.980	
	*Age (years)	-----	-----	-----		0.0005	0.0007	0.460	
	*Sex (female)	-----	-----	-----		-0.0284	0.0135	0.038	
	*Education (College degree or higher)	-----	-----	-----		0.0113	0.0124	0.366	

*Variable was forced in the model as covariate for the adjusted analysis.
Note: MVPA = Moderate-to-Vigorous-Intensity Physical Activity

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