

Effects of a Lifestyle Intervention on Brain-Derived Neurotrophic Factor (BDNF) in
Obese Latino Youth with Pre-Diabetes

by

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ABSTRACT

Latino youth have substantially higher rates of obesity and T2D than their white peers. The higher prevalence of obesity and T2D among Latino youth places them at greater risk for cognitive dysfunction, an urgent and serious health threat to the United States. Exercise has been the cornerstone to combat the negative effects of obesity, diabetes and recent research also supports this effects for preventing cognitive dysfunction. A wealth of evidence suggests that a mediating mechanism linking exercise with brain health is BDNF, a cognitive biomarker that increases in the brain with exercise. BDNF is the most abundant neurotrophic factor that supports growth, survival and synaptic plasticity of neurons, all vital for cognitive function and brain health. The present study sought to investigate the effects of a 12-week lifestyle intervention of physical activity and lifestyle education on serum BDNF, in obese pre diabetic Latino youth.

A total of twelve obese pre diabetic Latino youth were selected from a larger RCT sample to be the focus for this analysis. After an overnight fast, a serum concentration was collected from all youth to be used for the BDNF analysis. In addition, the following cardio metabolic measures were also at taken at baseline and post intervention:

Submaximal VO₂max, medical and family history questionnaire, anthropometric, fasting glucose and a 2-hour oral glucose tolerance test (OGTT). A 12-weeks Lifestyle Intervention that involved a progressive moderate to high intensity exercise component and lifestyle education program did not significantly change serum BDNF levels in obese pre diabetic Latino youth. In conclusion, the variation of our serum BDNF results are highly speculative at this time, therefore the need for future investigations is crucial.

DEDICATION

To Mi Familia, Tyler C. Smith, Dr. Ina Lieberman, Chioma Atanmo and study participants.

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CHAPTER 1

INTRODUCTION

Latinos in the United States experience more health inequalities compared to non-Hispanic Whites (1). The U.S. Office of Minority Health reported that in 2011, adult Latino Americans were 1.2 times more likely to be obese than non-Latino Whites. The most recent prevalence data on pediatric obesity suggests that 22.8% of Hispanic youth aged 12-19 years are obese (2). The pediatric obesity epidemic has contributed to the emergence of the type 2 diabetes (T2D) in children and adolescents (3). T2D is a complex disease that involves an interplay between social, behavioral, environmental and genetic risk factors. In genetically susceptible youth, poor diet and a sedentary lifestyle contribute synergistically to the premature development of T2D (4). Physical inactivity related disparities further contribute to an unbalanced disease risk burden among Latino youth who exhibit higher rates of prediabetes and T2D (5, 6). In addition, recent findings suggest that adverse health conditions are not limited to the physiological processes in the body. T2D is also linked to neurological ailments as evident by cognitive dysfunction in adults (7, 8, 9, 10), and these impairments are also evident in youth who are at high risk for developing T2D (11; 12). Adolescents who are obese and have T2D exhibit structural and functional impairments in their brain that is consistent with the cognitive decline in adulthood (13).

CHAPTER 2

REVIEW OF LITERATURE

Obesity, Diabetes, and Cognitive Function (CF)

The current rise in dementia cases among older adults has trended to parallel the rising rates of obesity in the United States (14). Obesity is associated with a faster cognitive decline across the human lifespan. Based on epidemiological studies, obesity has been linked to an increased risk for Alzheimer's disease (15, 16), and dementia (17; 14). Obesity has also been linked to long-term declines in cognitive performance even when detectable neurological disease is not yet present (18). Additionally, obese adults perform significantly lower on tasks assessing global cognition, attention (19); executive function and memory (20) compared to their normal weight counterparts (21). More alarming is the negative impact obesity has on cognitive deficits when it co-exists with a metabolic disease like T2D (22). Older Individuals with T2D are at 50-100% at greater risk of developing dementia, especially those with a longer history of T2D, less glycemic control and more vascular complications (23, 24). Unfortunately, cognitive impairment is not only present in the aging population, obese adolescents also exhibit cognitive dysfunction relative to their normal-weight peers (25). This is an emerging area of literature that aims to understand the relationship between obesity and cognition during adolescence and across the lifespan. In the few papers that have been published to date, evidence demonstrates overweight and obese adolescents perform worse than healthy weight adolescents in executive function tasks, specifically in areas that require greater

amounts of executive control (66). The observations have revealed differences in brain functioning as measured by functional neuroimaging and electrophysiological techniques suggesting that, healthy-weight children exhibit more efficient and denser patterns of neuroelectric activation relative to overweight/obese children in areas of executive control that require attention (28, 29), inhibition (30), and conflict monitoring (31). In addition, youth who are more fit also show differences in brain structure, as measured by magnetic-resonance imaging (MRI) voxel based morphomes (32, 33, 34)

Recent evidence indicates that metabolic disease risk may be a contributing risk factor to the differences seen in the brain structure and function of overweight/obese children. Children who exhibit at least one metabolic risk factor demonstrate lower performance in the executive control task, compared to healthy weight counterparts with no risk factors (35). In addition, Yau *et al.*, (36) observed differences in brain structure of obese children with one metabolic risk factor compared to healthy peers. These differences included smaller hippocampal volume and decreased white matter, both indicators of poor behavioral indices of attention, executive control and scholastic achievement. Morbidly obese adolescents with T2D perform significantly worse during executive function test and exhibit structural brain abnormalities compared to obese adolescents without T2D (13). Furthermore, obese youth with T2D demonstrate significant reductions in fast brainwave activity as measured via electroencephalograms (EEG), particularly in areas related to executive functioning such as the prefrontal cortex (37). Despite this growing area of inquiry, the relationship between obesity, diabetes, and cognitive function in children and adolescents remains poorly understood.

Potential Mechanisms Linking Cognitive Dysfunction with Obesity and Diabetes

To date, several models identify the mechanisms linking obesity and T2D to cognitive impairments. These mechanisms include, microvascular disease (22), disrupted glucose imbalances and impaired insulin signaling (38). Microvascular disease is caused by a variety of risk factors such as hypertension, T2D, hyperlipidemia and smoking. In addition to microvascular disease, these risk factors contribute to neurological diseases such as vascular dementia and Alzheimer disease. Hypertension in particular is the leading risk factor for cerebral microvascular complications such as stroke. In addition, an alteration in cerebral hemodynamics is directly linked to ischemic-related injury in the brain (39).

Glucose imbalances: Poor glycemic control may be one of the strongest contributors to adverse brain structural changes and cognitive impairments in obese individuals. Recent evidence suggests that the brain plays an important role in the maintenance of glucose homeostasis (40), via the downstream mechanisms of leptin-proopiomelanocortin (POMC) signaling pathway. Yaffe *et al.*, (41) found that older nondiabetic women with higher HbA1c levels, exhibited greater declines in cognition over time. Other work demonstrates that poor glycemic control adversely impacts the integrity of the brain. The hippocampus and the frontal lobes are the two areas of the brain that are most susceptible to alterations in glucose homeostasis (42). These alterations may cause learning and memory deficits in adults and in children. For instance, the hippocampus sensitivity to the glucose and insulin imbalances may lead to a neuronal synaptic reorganization and impairment (43, 44, 45). Poor glycemic control also

alters cognitive performance due to the increased production of advanced glycation end products (AGE) that contribute to inflammation, and damage in the cellular and molecular structures (46). The process of the normal aging brain is characterized by a decrease in cognitive performance, and structural brain changes. However, when it is coupled with obesity and T2D, cognitive decline advances at a faster speed (47). There is a need for additional work to better understand the effects of poor glycemic control on the structure of the brain and cognitive function of obese individuals prior to developing T2D.

A separate mechanism that aims to understand the effects of obesity and T2D on cognitive function is an increase of insulin resistance. Insulin resistance may stimulate the hippocampus to decrease insulin-stimulated translocation of glucose transported such as GLUT-4. This may result in dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) (48). One of the main roles of the HPA axis is to control stress reactions. Higher levels of chronic stress accelerate inflammatory markers that have been linked to cognitive deficits in obese individuals (49). Although, there are different possible mechanisms linking obesity and T2D with cognitive impairment, the casual relationship remains unclear (50).

Exercise is the Cornerstone for Treating and Preventing Obesity, Type-Two Diabetes (T2D) and for Improving CF

One of the most powerful and effective cognitive enhancers is physical exercise (51). Increases in physical exercise combined with improvements in dietary habits represent the cornerstone for preventing diabetes. In particular, exercise has the capacity

to not only reduce diabetes risk but can improve cognitive function in a dose-dependent manner. (52). Improvements have been in a variety of species, for different memory tasks (53), neurogenic and neurotropic activity in the brain. The neuroprotective effects of exercise include enhanced brain structure and function across the lifespan (125; 54, 55). Exercise training leads to an increase attention and performance on cognitive tasks related to executive function (56) and facilitates the development of adaptive, goal-directed problem-solving skills (57). The interplay between obesity, exercise and brain function is executive function (explained in the next section) where the cognitive processes that are associated with monitoring and controlling both thought and goal-directed behaviors are housed (58). Regular participation in physical activity among preadolescent children is associated with improved cognition, particularly in the domains of executive function, learning, and memory (59)

Executive Function (EF) is the umbrella of fundamental cognitive processes and skills that are essential for mental and physical health (60). Among youth, executive function is necessary for academic achievement, and for appropriate social and psychological development (60, 61). There are three core areas of EF which include, inhibitory control (resisting distractions or habits to maintain focus), working memory (mentally holding and manipulating information), and cognitive flexibility (multi-tasking). These three areas work collectively as well as independently depending on the task or behavior (57, 62). The prefrontal cortex (PFC) is the main area of the brain involved with EF and each core EF area belongs to a PFC sub-region. Unlike other regions of the brain, the PFC matures in late adolescence and early adulthood (63).

Exercise Neurological Impact

The three current hypotheses that exist to explain how exercise may impact neurological status in the areas of executive function and cognitive health include, 1) enhancement in oxygen saturation in the areas of the brain that are crucial for cognitive performance, such as the PFC and hippocampus 2) increases in neurotransmitters that act as chemical messengers for communication between neurons (64) and 3) upregulation in neurotrophins such as brain-derived neurotrophic factor (BDNF) that promote neuronal growth, survival and synaptic connectivity (65). The positive impact of exercise on cognition among youth is an area of importance as childhood is a critical period for the development of brain function, structure and connectivity and changes in these parameters can have lifelong implications (66).

Chaddock-Heyman *et al.*, (109) conducted a randomized control trial to assess the influence of a 9-month physical activity program on task-evoked brain activation during childhood by using functional magnetic resonance imaging (fMRI). Children in the intervention group engaged in physical activity classes for 60 minutes, 3 times / week for 9 months, while the wait-list control group was given the opportunity to participate in the intervention the following year. Compared to the wait-list control group, the intervention children showed a greater activation in the prefrontal cortex and performed higher on an executive function task. These results suggest that exercise is important for the development of brain and cognition during childhood.

Brain Structures in Humans

The influence of physical activity on cognition has been shown to be influential by enhancing areas related to executive control (66). The frontal lobe, prefrontal cortex (PFC) is the region of the brain where executive function skills are derived (67; 68). The PFC is jointly connected to the basolateral amygdala; the two structures are associated with decision-making processes that play an important role in impulsivity and compulsive choices (69). It is widely known that there are other areas in the brain that are involved in executive function including the dorsolateral PFC, the anterior cingulate cortex, the orbitofrontal cortex, and the medial PFC (70). These areas have extensive functional connections to other regions of the brain including the subcortical areas and brain stem which control the automatic systems that contribute to executive function (71).

Exercise Benefits for Children and Adolescents

Multiple studies (66, 72 and 73) and reviews (65 and 74) have been conducted to assess the influence of physical activity or exercise and executive function skills in children. The most recent, Hillman et al. (66) investigated the effects of a 9-month, randomized control physical activity (PA) program (Fitness Improves Thinking [FITKids]) on brain and behavior during tasks requiring attentional inhibition and cognitive flexibility among 221 children between 7-9 years of age. They hypothesized that, relative to a waiting list control group, the FITKids intervention would result in improved behavioral performance, increased attention allocation, and faster cognitive processing speed. In addition, the authors predicted a positive correlation between participation in the intervention and improvements in executive function skills as markers

of cognitive function. Among the intervention group, the results did demonstrate significant improvements in fitness, cognitive inhibition, and cognitive flexibility both markers of EF. The authors concluded an enhancement of cognitive performance and brain function during tasks requiring greater executive control, which provides support that PA can improve cognition and brain health in children. The authors suggested that their findings broaden the relevance for public health, the educational environment, and the context of learning.

Brain Derived Neurotrophic Factor (BDNF) and Exercise

Brain Derived Neurotrophic Factor (BDNF) is an essential neurotrophin encoded by the BDNF gene and transcribed with the signaling of its receptor tyrosine kinase TrkB. BDNF supports brain plasticity and health, through its involvement in regulating survival, growth and maintenance of neurons (76). In addition, BDNF is closely connected with central and peripheral molecular processes of energy metabolism (77, 78), learning, and memory (79). It has been well established that BDNF synthesis is centrally mediated and activity dependent (80) where exercise can upregulate transcription levels in the brain (81). Although exercise is associated with a cascade of molecular and cellular processes that support brain plasticity and health, it was not until the 1990s that research began to explore the possible mechanisms linking exercise with brain health. One of the mayor breakthroughs started to investigate the effects of acute exercise and/or training on BDNF levels in animals (82, 83, 84, 65, 85, 86) and nearly a decade later in humans (87).

Voluntary running results in significant upregulation of BDNF mRNA and

protein concentrations (88, 81, 82). Animal studies report the highest levels of BDNF to exist in the hippocampus (89), a critical area for learning and memory. To demonstrate the importance of BDNF in these processes, it has been reported that BDNF knock-out mice demonstrate deficits in spatial memory, learning and hippocampal Long Term Potentiation (LTP). LTP a model for the processes that may underlie the strength of information for long term storage within the synaptic neuronal networks (90). In addition to the functional role BDNF plays in the hippocampus it also contributes to hippocampal structure by increasing grey matter, which is crucial for maintaining life-long neurological health.

Physical Activity stimulates BDNF production in an intensity-dependent manner (91, 92). A systematic review of acute aerobic exercise trials found that moderate and high intensity bouts of exercise increase circulating BDNF levels (93). To date, the most studies investigating the effects of PA on BDNF have focused on clinical populations and the role BDNF plays on mental disorders such as schizophrenia (87), Alzheimer's disease, and depression or anxiety (94). Recent evidence suggests that BDNF plays an important role in the maintenance of glucose homeostasis (95, 96, 97). However, the degree to which BDNF is associated with T2D remains uncertain. Some reports indicate that circulating BDNF levels are lower in T2D compared to healthy counterparts (98, 96), while others have found the opposite (99). Three major factors that may explain the inconsistencies include the time point of measurement, the exercise protocol and the differences in populations across studies in terms of sex, age, and body-weight (100). These factors notwithstanding, the data more consistently show that among individuals

with T2D, peripheral BDNF levels decrease as length of disease increases (98).

Preventative Measures of Obesity, T2D and Cognitive Dysfunction in Latino Youth

Latino youth have substantially higher rates of obesity and T2D than their white peers. The higher prevalence of obesity and T2D among Latino youth places them at greater risk for cognitive dysfunction. These negative health effects on Latino youth and the nation as a whole cannot be overlooked, as Latinos currently represent the most populous and fastest growing ethnic minority in the United States. In the years ahead, the negative health effects experienced in Latinos will likely affect the nation as a whole, resulting in greater health care expenditures, higher rates of metabolic and neurological diseases, loss of work productivity, and stunted educational academic achievement and economic growth. Therefore, preventative measures are needed to stop the negative ripple effects of obesity, T2D and cognitive dysfunction in Latino youth. Exercise has been a cornerstone for the prevention of obesity and T2D. In addition, recent evidence, has identified exercise as one of the most powerful and effective enhancers for cognitive function. Cognitive function across the lifespan is essential for learning and memory, goal setting and academic and career success in life.

A wealth of evidence suggests that a mediating mechanism linking exercise with brain health is BDNF, a cognitive biomarker that increases in the brain with exercise. BDNF is the most abundant neurotrophic factor that supports growth, survival and synaptic plasticity of neurons, all vital for cognitive function and brain health. The majority of data examining the effects of exercise on BDNF comes from studies of animals or in adults whereas evidence on the effects of exercise on brain health is focused

on improvements in cognitive processes. No study has investigated the effects of exercise on BDNF in obese pre-diabetic Latino youth. Therefore, the purpose of my master's thesis is to investigate the effects of a lifestyle intervention (physical activity and nutrition) on BDNF, a biomarker of cognitive health in obese Latino pre-diabetic youth. We hypothesize, that a 12-week lifestyle intervention of (physical activity and nutrition) will result in significant increases of serum BDNF compared to baseline.

CHAPTER 3

METHODS

Participants

Effects of a lifestyle intervention (physical activity and nutritional education) on BDNF serum concentrations were investigated using a quasi-experimental, pre-test, post-test design. The current intervention is a subset from the larger study described in more detailed in Williams *et al.*, 2016. For the purpose of the present investigation, a total of 12 pre-diabetic obese (BMI percentile \geq 95th percentile for age and gender or BMI \geq 30 kg/m²) Latino Youth (self-report by parents) were included in the analyses (7 girls (BMI = 34.8 ± 6.0 kg/m²) and 5 boys (BMI = 32.3 ± 3.2 kg/m²) all between the ages of 14 and 16 years (15.4 ± 1.1 years). The youth were recruited to participate in the ASU ELSC lifestyle Intervention from churches, health clinic and schools in the local Phoenix metropolitan area. Serum samples of youth who participated in the intervention of the larger study but were not identified as pre-diabetic, and pre diabetic youth who did not complete a minimum of 75% participation/attendance in the intervention, or did not give consent for additional analysis were also excluded from the BDNF analysis. Due to ethical practices, all youth who were diagnosed as pre-diabetic at screening were not randomized, and were automatically placed in the intervention. Therefore, no pre-diabetic youth were included in the control group. The study was approved by Arizona State University's Institutional Review Board. All participants and their parents provided informed written consent prior to any procedure.

12-Week Lifestyle Intervention: Lifestyle Curriculum

The ELSC intervention was developed through the team's extensive experience working with obese Latino youth and our review of the literature. Components of the intervention are based upon enhancing key constructs of Social Cognitive Theory (SCT) including self-efficacy and fostering social support. The intervention is delivered in the community by bilingual/bicultural *Promotoras* (health educators) to adolescents and their families. *Promotoras* deliver weekly education classes in groups that focus on family history and obesity-related health risks, healthy eating, family roles and responsibilities, physical activity and inactivity, and emotional well-being. Participants are presented with their baseline clinical metabolic measures and this information is used to initiate the discussion on making healthy lifestyle choices. Participants learn behavior change strategies such as goal setting, self-monitoring, decision-making, and positive self-imagining the power of positivity as they pertain to the following class sessions, health risks, culturally-appropriate nutrition education (i.e. healthy meal planning, reducing sugar and fat intake, increasing fiber intake, eating breakfast, portion sizes / snacking), physical activity, self-efficacy for making healthy nutrition and physical activity choices, self-esteem, and a final wrap-up session on sustaining a healthy and balanced lifestyle. Children and parents are asked to complete a behavioral contract at the beginning of the program and readiness to change is documented and discussed. Classes are delivered using an interactive format where youth and families are encouraged to share their personal experiences, beliefs, successes, and challenges. Out of class activities such as grocery shopping with parents to prepare a healthy family meal are used to facilitate curriculum integration into day-to-day lifestyle changes. Throughout the program, youth

and their families are asked reflection questions of how they incorporated information learned into their everyday life (e.g. *What did you do last week to improve how you feel about yourself?*). Success is recognized and acknowledged and challenges are discussed with a focus on strategies to overcome barriers. At the conclusion of the program, youth are presented with a certificate of completion and are applauded for their efforts by the *Promotoras*, families, peers, and research team.

12-Week Lifestyle Intervention: Physical Activity

The physical activity component includes structured and unstructured exercise 3 days/week for approximately 1-hour. The structured component includes both aerobic and resistance exercises that are progressive in nature with the first 2-4 weeks focusing on motor skill acquisition, exercise confidence, and developing a fitness base. Aerobic exercises include various group activity classes (e.g. spinning and basketball) delivered by YMCA instructors with the goal of maintaining average heart rates > 150 BPM. This high-intensity physical exercise has been shown to significantly improve cardiovascular fitness and other metabolic markers in obese youth (102). Heart rate monitoring and rate of perceived exertion were used to monitor and document exercise intensity throughout the program. Resistance exercise includes circuit training using age and size appropriate equipment. Resistance training is incorporated because previous studies suggest this form of exercise is both enjoyable and metabolically beneficial for obese youth (103).

Unstructured exercises include team sports, games, and activities that promote social support, encouragement, and bonding among youth. We have observed significant heterogeneity in baseline fitness, activity levels, and exercise experience so youth are

encouraged to work at their own pace and support their peers at all levels. Healthy competition is encouraged but any negativity or teasing is immediately addressed on an individual and group level. Adolescents are encouraged to utilize the YMCA outside of the intervention and the YMCA will make special membership arrangements for families participating in the project.

Cardiovascular Measures: Submaximal VO₂ max

Youth were tested with a Submaximal VO₂max treadmill-based protocol by Ebbeling *et al.*, (104) that was later validated to accurately predict maximal VO₂ in obese children and adolescents (105). Resting heart rate (resting HR), in beats per minute (bpm) was obtained immediately before starting the test. Participants began to practice walking on the treadmill at a self-selecting walking pace and at 0% grade for an initial 4-minute phase. Immediately after the first 4 minutes, the grade was increased to 5%, maintaining the same speed for 4 more minutes. The HR as reported by the heart rate monitor watch was recorded at the end of the 8 minutes and entered into the prediction equation. The VO₂max values were measured in mL·min⁻¹.

Cardiovascular Measures: Fasting Glucose and 2-Hour OGTT

All participants completed baseline and post intervention assessments at the ASU Clinical Research Unit at ~8:00 am after an overnight fast. These measures included a medical and family history questionnaire, anthropometric (height, weight and waist circumference measure to the nearest 0.1 cm, 0.1 kg, 0.1 cm respectively), and a 2-hour oral glucose tolerance test (OGTT). The OGTT is a measure of diabetes risk. Participants ingested an oral glucose tolerance beverage of 75 grams of glucose solution and blood

samples were obtained six times for a period of 2-hours to determine plasma glucose concentrations (glucose oxidase, YSI INC., Yellow Springs, OH). These results detect if impaired glucose tolerance is present, which classifies the participants as pre-diabetic. According to the American Diabetes Association pre-diabetes is determined as having an OGTT equal or greater than 140 mg/dL to 199 mg/dl. A fasting sample collected prior to the OGTT was used to evaluate serum BDNF levels at baseline and post intervention.

Cognitive Biomarker: BDNF Procedures

The blood samples drawn at baseline, and post intervention (estimated 15 hours post moderate to high intensity exercise session and 10 hours of fasting) will be centrifuged at 3000 rpm to obtain serum. Serum will be frozen and stored at -80 °C until assayed to determine the serum BDNF concentrations. Serum samples will be taken out of the freezer to allow samples to reach room temperature for 150 minutes. Samples are mixed in the vortex before centrifugation for 15 minutes at 3000 x g. The serum samples require at least a 20-fold dilution into Calibrator Diluent RD6P prior to the assay. Utilizing the suggested 10 uL of sample + 190 uL of Calibrator Diluent RD6P. Samples will be analyzed in duplicate using the commercial enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA #DBD00).

Statistical Analysis

We conducted a Paired Sample T-Test examining pre and post differences for our primary measure, serum BDNF and for other cardio metabolic markers and fitness levels of each participant. We chose a p value maximum of 0.05 to demonstrate significance. Correlational analyses were also conducted to analyses the relationship between changes

in BDNF and changes in other cardio metabolic variables. Pearson's correlation for associations between changes in serum BDNF and BMI, fitness and diabetes risk factors.

CHAPTER 4

RESULTS

Cognitive Biomarker: Serum BDNF

A 12-weeks Lifestyle Intervention that involved a progressive moderate to high intensity exercise component and lifestyle education program did not significantly change serum BDNF levels in obese pre diabetic Latino youth. We conducted a pair sample T-test for serum BDNF levels at baseline ($21050.8 \pm 5911.$) vs post-intervention (21850.3 ± 6054.7) Pair Sample T-test $p = .7$ (*Fig. 1*). Analyzing baseline data from all participants, serum BDNF levels were comparable in males vs. females (males $20,083.3 \pm 4,586.4$, females $21,717.8 \pm 6,978.4$ pg/mL, (see *Table 1* for additional variables between gender).

Lifestyle Intervention: Demographics + Cardio Metabolic Assessments

Participants demographics, fitness and glucose baseline and post-intervention data are provided in *Table 2*. These data demonstrate that the 12-week lifestyle intervention had significant changes in 2-hour glucose values from (151.0 ± 9.2 to 123.4 ± 31.5 ml/L $p < .007$), BMI (33.7 ± 5.0 to 33.2 ± 5.1 $p < .016$), and Fat percentage (44.4 ± 4.9 to 40.5 ± 6.6 $p < .004$). However, it did not have significant changes in weight (90.0 ± 10.8 to 89.6 ± 11.5) $t(11) .72, p < .85$. Submaximal V_{2max} Fitness assessments were statistically significant (2398.5 ± 660.2 to 2859.6 ± 399.2) $p = .05$. In addition, *Graph 1* demonstrate the average heart rate (HR) bpm of the entire cohort for each week of the physical activity classes. The average HR for the intervention was 160 bpm which meets the goal of 150 bpm (classified as high intensity based on HR max for this age group) for the

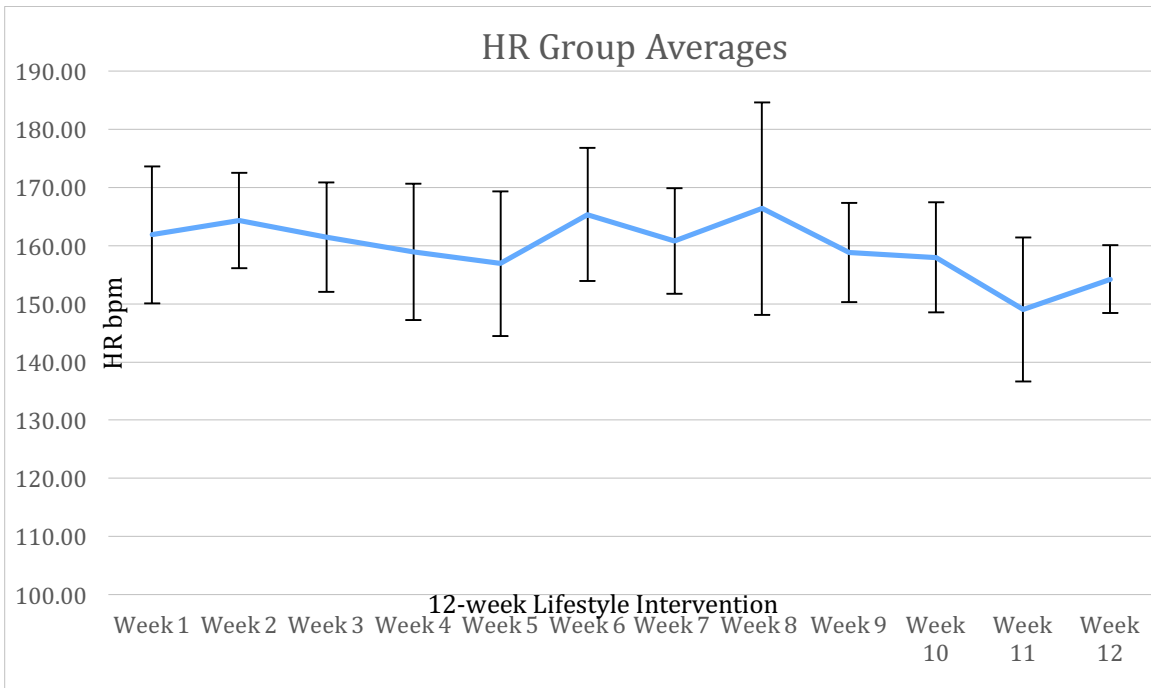
intervention's exercise intensity levels for all participants. *Table 6* demonstrate the correlation data for changes in serum BDNF and measure of BMI, fitness and diabetes risk factors. We did not find any correlations.

Table 1. Baseline Gender Differences*

T1	Female	Male	Total Participants	<i>p</i> <.05
Gender	7	5	12	
Age (years)	15.8 ± 1.0	14.9 ± 1.2	15.4 ± 1.2	
Weight (kg)	90.9 ± 12.9	88.7 ± 8.3	90.1 ± 10.8	.7
BMI (kg/m²)	35.1 ± 6.0	31.7 ± 2.5	34.2 ± 4.9	.3
BMI %	97.8 ± 1.9	98.5 ± 0.9	98.2 ± 1.9	.5
Fasting Glucose (mg/dL)	86.3 ± 9.3	88.6 ± 8.8	86.6 ± 8.9	.7
2-hour Glucose (mg/dL)	149.4 ± 11.3	153.2 ± 5.6	150.4 ± 9.4	.5

*Data is shown as mean ± SD values with *p* values < .05 are significantly different.

Graph 1. Cohort Heart Rate (HR) bpm Averages*



*Data is shown as group HR averages (bpm) ± SD values for each week. Desired group HR averages per week: 150 bpm.

Table 2. Pre & Post Cardio Metabolic Values*

	Pre N = 12 bpm	Post N = 12	p-value
BMI (kg/m ²)	33.70 ± 5.01	33.18 ± 5.2	.02
Fasting Glucose (mg/dL)	87.25 ± 8.8	84.75 ± 8.2	.09
2-hr Glucose (mg/dL)	151.00 ± 9.2	123.42 ± 31.5	.01
Fitness - VO2max (mL*min ⁻¹)	2398.5 ± 660.2	2859.6 ± 399.2	.05

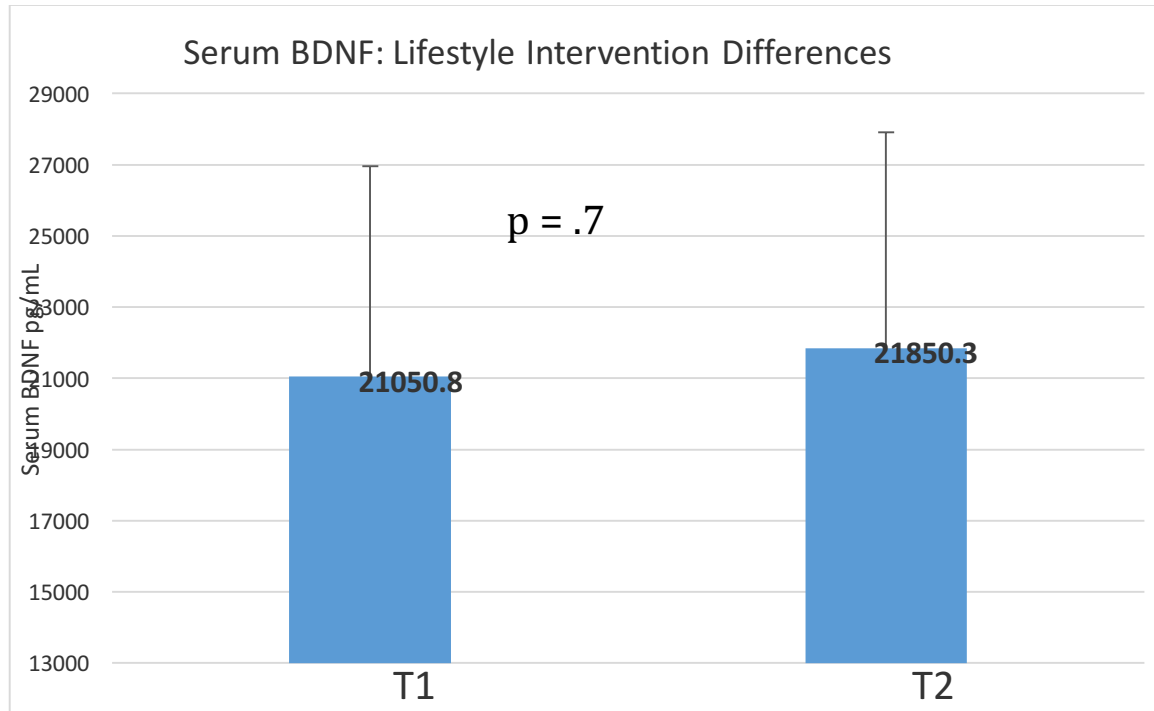
*Data is shown as mean ± SD values with p values < .05 are significantly different.

Table 3. Individual Changes in BMI*

Sample ID N = 12	Pre: BMI	Post: BMI	BMI Change
003-1	35.8	34.8	-1.0
010-1	34.1	33.8	-0.3
015-1	33.2	32.6	-0.6
021-1	37.5	37.9	0.4
032-1	29.2	28.5	-0.7
059-1	32.8	33.3	0.5
124-1	30.7	30.0	-0.7
130-1	28.2	27.2	-1.0
134-1	34.6	32.9	-1.7
142-1	46.4	45.9	-0.5
158-1	27.8	26.9	-0.9
164-1	34.1	34.3	0.2

*Data is shown as individual pre and post BMI (kg/m²) values and the BMI change after the 12-week lifestyle intervention for each participant.

Figure 1. BDNF Pair Sample T-Test*



*Data is shown as mean serum BDNF (pg/mL) group changes values post 12-week lifestyle intervention compared to baseline.

Table 4. Individual Changes in BDNF *

Sample ID N = 12	Pre: BDNF	Post: BDNF	Change in BDNF (pg/mL)
003-1	30,969.5	29,386.2	-1,583.3
010-1	27,687.5	30,283.5	2,596.0
015-1	17,143.1	21,411.1	4,268.0
021-1	23,164.9	25,058.2	1,893.9
032-1	8,359.1	23,735.7	15,377.7
059-1	19,965.8	23,168	3,202.2
124-1	15,896.6	8,026.9	-7,870.7
130-1	23,509.8	14,327.8	-9,182.0
134-1	20,223.8	19,823.5	-400.3
142-1	25,932.7	24,281.9	-1,651.8
158-1	19,723.8	22,179.1	2,455.2
164-1	20,032.7	20,521.4	489.6

*Data is shown as individual pre and post BDNF (pg/mL) values and the BDNF change after the 12-week lifestyle intervention for each participant

Table 5. Additional Analysis for Each Participant*

Sample ID	Average Attendance (%)	Average HR (bpm)	Attendance on Friday (1) before T2 lab appointment	Change in BDNF (pg/mL)
003-1	94	153.9	1	-1583
010-1	100	160.9	1	2596
015-1	86	150.0	1	4268
021-1	86	162.0	0	1893
032-1	81	165.6	0	15377
059-1	94	168.3	1	3202
124-1	94	155.8	1	-7870
130-1	86	164.8	1	-9182
134-1	81	163.9	0	-400
142-1	81	151.1	0	-1651
158-1	97	149.7	1	2455
164-1	75	172.3	1	489

*Data is shown as individual analysis for different values that may have influenced the serum BDNF (pg/mL) for each participant.

Table 6. Correlations of BMI, Fitness and Diabetes Risk Factors with Changes in Serum BDNF*

Changes	BDNF (pg/mL)	P-value (<0.05)
BF%	-.11	.74
BMI (kg/m ²)	.20	.52
BMI percentage	.11	.73
Fitness: VO2max (mL*min ⁻¹)	.07	.86
Fasting Glucose (mg/dL)	.49	.10
2-hr. Glucose (mg/dL)	.34	.28
Attendance	-.15	.65
HR Averages (bpm)	.14	.68

*Data is shown as group analysis for different values that may have correlation with the serum BDNF (pg/mL), values with p values < .05 are significantly correlated

CHAPTER 5

DISCUSSION

Exercise stimulates learning, survival of hippocampal neurons and neuronal synaptic plasticity. Recent evidence linked BDNF as one of the primary contributors of exercise benefits on the brain (106). To our knowledge, we are the first to investigate the effects of a lifestyle intervention on serum BDNF levels in pre-diabetic obese Latino youth. Our results did not show any significant change in serum BDNF levels following a 12-week Lifestyle Intervention (Physical activity and lifestyle education) *Fig. 1*. Exercise training has been shown to increase BDNF levels not only in the brain, but also in the periphery through its high-affinity receptor, tyrosine kinase (TrkB) in response to acute exercise. The exercise response to BDNF synthesis and storage remain undetermined. However, based on the literature 70-80% of serum BDNF may derived from the brain at rest, 2-4 hours after the exercise (107). The rest might be released when induced by exercise from the platelets (111) and additional evidence demonstrated for BDNF to be synthesized in the contracting muscle, however it was not shown for the levels to be released into the circulation, instead these levels increase muscle metabolism (112). The BDNF increases due to exercise have been shown to be widely dependent on time of measurement post exercise. Previous studies have shown BDNF levels to peak immediately after moderate to high intensity acute exercise, and levels decline, reaching baseline levels at 24 hours post exercise (113). Same review also demonstrated increases of serum BDNF levels for long lasting aerobic exercise programs performed above 60% intensity. However, as show in acute exercise studies, the levels returned to baseline and were not long-lasting. We collected serum samples at an estimated 16-hours after the last

exercise session, therefore, any potential significant increases of the serum BDNF may have already returned to baseline by the time we took the measurement. That could have been one of the possible reasons why we did not see significance.

To date, little is known about the sustainability of exercise induced BDNF levels and to what extent of time do the effects prevail as it relates to cognitive function and under which timeframe and conditions do these effects vanish. In addition to measurement time point, exercise intensity has been reported to have a strong effect in the BDNF levels. First reported by Ferris *et al.*, (91) serum BDNF to be exercise intensity-dependent at levels higher than 75% of VO₂max compared to the control group that exercised at 55% intensity. As reported in *Table 5*, our participants did reach the desired intensity. Animal studies have demonstrated for BDNF to cross the blood-brain barrier in both directions, proposing that serum BDNF do reflect BDNF levels in the brain (108). Normal values for resting BDNF concentrations are unclear, however based on previous work from a large sample of healthy adults reported to have 22,600 pg/mL (113). Our participants showed BDNF resting levels averaging 21,850.3 pg/mL slightly lower than the considered normal levels in healthy adults. It has been suggested for BDNF levels to increase as a compensatory mechanism in the pathogenesis of metabolic disorders (116) therefore it is possible for pre diabetic youth as shown in our study to have near considered normal levels of BDNF. However, the improvement of cardiovascular risk parallels the decrease of peripheral BDNF concentrations (11, 119). BDNF levels also have an inverse relationship with age and weight (113), with obese diabetic adults (98), and with obese youth (115). Considering these associations, the

importance of larger well-designed studies is needed to further investigate the effects of exercise on BDNF levels and its effects in cognitive function in at high risk populations, who are well on their way at developing T2D and or learning and mood disorders at an earlier age.

To date, human observational studies have not controlled for possible lifestyle confounders such as nutrition or sleep. Patients with neurodegenerative diseases and psychological disorders including depression, post-traumatic stress, autism, schizophrenia, bipolar disorder addiction and attention-deficit hyperactivity disorder have also been shown to have lower levels of BDNF (120). Childhood and adolescence are a critical developmental period where neuronal programming for behavior is established (110). Our findings are in agreement with a study that demonstrated unaltered serum BDNF levels in T2D adolescents with similar age group, and timing of the measurement. However, to the authors surprise their control obese group did have significant changes after the 12-week moderate to high intensity exercise program (114). Based on other research it demonstrates that newly diagnosed T2D groups have elevated levels of serum BDNF (116) and similarly to CVD, BDNF levels lower as T2D progresses (117). Pareja-Galeano *et al.*, (102) was the first to report the effects of exercise training on peripheral BDNF levels in healthy adolescent boys. Emphasizing the importance and impact of exercise training during adolescence.

Empirical research aiming to better understand the cognitive and neuronal development during puberty and adolescents has shown significant functional differences in all areas of executive function and PFC structural changes. Puberty represents a time

period where neuronal re-organization is undergoing development, which may influence executive function and social cognition during this period (27). A pilot cross sectional study investigated for the first time the variations of BDNF levels related to pubertal stages in plasma of healthy children and adolescents. It reported BDNF levels to be significantly lower from midpuberty to high puberty compared to prepuberty to mid puberty in females and higher in prepuberty in males. There were no significant differences between females compared to males (121). We did not measure for puberty status in our youth. Moreover, any lifestyle influence such as exercise that increases BDNF and influences cognition, could be a guiding force in the regulation of neuronal growth and prevention of psychiatric and neurological diseases during this period and in adulthood.

There are several lifestyle factors in addition to exercise that have shown to have an association with serum BDNF levels. Factors that influence healthy levels of BDNF in healthy adults are; appropriate amounts of sleep, low levels of inflammation and stress, fruit and vegetable intake, low saturated fat meals and lower daily average of television watching (26). It is possible that our population may have been negatively influenced by one or more of these lifestyle factors after their exercise session and before attending the lab for the collection of the serum sample. Youth who participated in our study have anecdotally reported having less sleep and being stressed due to school projects, watching television or playing video games at night, and eating foods like pizza or fried foods which contain higher amounts of saturated fat. In contrast meals with high amount of omega-3 fatty acids increases BDNF levels and has greater influence in brain health. We

have to keep in mind that the youth who participated in our intervention are all high school students, their stressors can also range anywhere from emotional instability, break-ups with significant others, to homework, sleep and family issues. We did not measure for these lifestyle factors, which leaves us to speculate that the 16-hour window between the last exercise session and the time we collected their serum sample could have been influenced by one or more of these factors. Future research should account for these factors.

Notwithstanding the results, there were several limitations to the present investigation. First, we were not able to compare our results to a control group due to our quasi-experimental design. Second, our sample size was small for the BDNF measures which may have decreased the strength of our statistical analysis, however it was big enough to demonstrate significant improvements in cardio metabolic markers due to the intervention. Third, the original study was designed to target youth at risk for developing T2D not youth who also had cognitive dysfunction or neurological disorders. Future research should explore the effects of exercise in pre-diabetic obese Latino youth who have well-characterized mood and learning problems or youth who have been clinically diagnosed with psychological disorders or neurological disease. Fourth, we did not include measures for brain imaging or cognitive function assessments to compare the exercise effects with cognitive function. Consequently, more research is needed.

It is critical to continue to explore the effects of exercise in serum BDNF levels and cognition in pre-diabetic Latino youth since this population is placed at higher risk to develop diabetes and cognitive dysfunction which have the potential to be a burden to

society in healthcare cost and loss of academic and work productivity. Scientific evidence that addresses the impact of physical activity programs for children's physical health, cognitive function, and overall psychological wellbeing is of critical importance. For youth, aerobic exercise is positively associated with academic achievement and performance in school (56). The shift from cognitive to physical focus in the literature has increased the need to educate school administrators, and policy makers who have reduced physical activity programs for children in trade for the demands of preparing children for standardized test. The many questions concerning the relation between exercise and children's cognitive functioning remains unanswered. One key area of research focuses on the potential benefits of the specific aspects of exercise (type, duration, or intensity) may have in cognitive enhancements (122). The literature supports the notion of participation in physical activity programs without negatively impacting children's academic performance rather support that systematic exercise programs may actually enhance the development of specific types of mental processing known to be important for meeting challenges encountered both in academics and throughout the lifespan (123; 124). Tomporowski *et al.*, (123) determined that exercise-training programs do not only enhance physical health, but may have an important aspect at improving children's areas of cognitive control and social development.

Despite the extensive amount of studies demonstrating the effects of exercise on BDNF levels in adults, we had a limitation to compare our results with studies involving adolescents. Although there are many missing links to fully understand the plausible effects of exercise on cognition and brain health in this population, current neuroimaging

and non-human molecular and cellular research suggest that aerobic exercise is an important lifestyle factor that influences cognitive function throughout the lifespan.

CHAPTER 6

CONCLUSION

In conclusion, the variation of our serum BDNF results are highly speculative at this time, therefore the need for future investigations is crucial. It is highly recognizable that exercise participation has the potential of improving brain health and preventing neurological disease. Determining the role exercise and BDNF regulation have in youth will provide with robust strategies for the development of therapeutic and preventative measures to take for the prevention of neurological disease and cognitive dysfunction in people through their lifespan.

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