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Gender and racial/ethnic differences in physiologic responses in the Stimulant Reduction Intervention using Dosed Exercise Study

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Abstract

Exercise may be beneficial for individuals in substance use disorder (SUD) treatment given the higher rates of both medical and psychiatric comorbidity, namely mood and anxiety disorders, compared to the general population. Gender and/or racial/ethnic differences in health benefits and response to prescribed exercise have been reported and may have implications for designing exercise interventions in SUD programs.

Method: Data are from the National Drug Abuse Treatment Clinical Trials Network (NIDA/CTN) Stimulant Reduction Intervention using Dosed Exercise (STRIDE) trial. Gender differences across racial/ethnic groups in physiological responses and stimulant withdrawal severity across time were analyzed using linear mixed effects models.

Results: Males completed significantly more exercise sessions than females and were more adherent to the prescribed exercise dose of 12 Kcal/Kg/Week. Controlling for age, race/ethnicity, treatment group and stimulant withdrawal severity, there was a significant gender by time interaction for body mass index (BMI) ($p < 0.001$), waist circumference ($p < 0.001$) and heart rate measured prior to exercise sessions ($p < 0.01$). For females, body mass index (BMI) and waist circumference increased over time while for males BMI and waist circumference stayed unchanged or slightly decreased with time. Heart rate over time significantly increased for females at a higher rate than in males. Stimulant withdrawal severity was similar in males and females at baseline but males exhibited a significant decrease over time while females did not.

Although baseline differences were observed, there were no time by race/ethnicity differences in physiologic responses.

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Conflict of interest

The authors have no conflicts of interest.

Discussion: Gender differences in response to exercise may have implications for developing gender specific exercise interventions in SUD programs.

Keywords

stimulants; exercise; gender differences; physiologic measures

1. Introduction

Regular exercise is medically recommended to lower the risk of several chronic health disorders such as high blood pressure and cardiovascular diseases, stroke, type 2 diabetes, metabolic syndrome and certain cancers. For substantial health benefits the Center for Disease Control (CDC) recommends adults do at least 150 minutes a week of moderate-intensity, or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity (USDHHS, 2018). In addition to the many physical health benefits, exercise has been shown to improve sleep, cognition, mood, quality of life, and anhedonia, and reduce substance use and cravings (Blumenthal et al., 2007; Chang, Labban, Gapin, & Etnier, 2012; Dolezal, Neufeld, Boland, Martin, & Cooper, 2017; Kvam, Kleppe, Nordhus, & Hovland, 2016; Ploughman, 2008; Rawson et al., 2015; Roberts, Maddison, Simpson, Bullen, & Prapavessis, 2012; Vidoni et al., 2015; Y. Zhou, M. Zhao, C. Zhou, & R. Li, 2016; Zschucke, Gaudlitz, & Strohle, 2013). A recent meta-analysis of the impact of exercise on substance use disorders (SUD) found that exercise significantly increased abstinence rates ($OR = 1.69$) and reduced withdrawal ($SMD = -1.24$), anxiety ($SMD = -.31$) and depression ($SMD = -.47$) symptoms. There were no differences regarding type of exercise or intensity of exercise. However, these beneficial effects diminished during follow-up if the exercise was not maintained (Wang, Wang, Wang, Li, & Zhou, 2014). Patients with SUD compared to the general population are at higher risk for comorbid medical and psychiatric disorders, specifically mood and anxiety disorders which disproportionately affect women (Bahorik, Satre, Kline-Simon, Weisner, & Campbell, 2017; Campbell, Barbosa-Leiker, Hatch-Maillette, Mennenga, Pavlicova et al., 2017, Schulte & Hser, 2013). As such, including exercise in SUD treatment programs may provide a number of benefits that go beyond SUD recovery, particularly for females. For example, exercise for female smokers may be particularly appealing as post cessation weight gain and negative mood are major concerns that create barriers to smoking cessation (Linke, Ciccolo, Ussher, & Marcus, 2013).

Although exercise has been explored for its efficacy in reducing drug use, it is not clear whether various other responses to exercise differ by gender and race/ethnicity. Rates of obesity in the US for adults 20 years of age and older have been steadily increasing from 19.4% in 1997 to 33.7% in 2008 to 39.6% in 2016 (Hales, Fryar, Carroll, Freedman, Aoki, et al., 2018; Hales, Fryar, Carroll, Freedman, & Ogden, 2018). Additionally, this increase was found to be greater among females and in certain racial/ethnic groups.

In females, rates of obesity are higher in non-Hispanic African Americans (AA) and Hispanics than in non-Hispanic Caucasian (Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016; Hales, Fryar, Carroll, Freedman, Aoki, et al., 2018; Moore-Greene, Gross,

Silver, & Perrino, 2012). Obesity is linked to higher risk of chronic diseases including hypertension, coronary heart disease, type 2 diabetes and certain cancers. The relationship between obesity and SUD is unclear as use of certain substances or recovery from SUD may affect taste preference, appetite and eating behavior (Cowan & Devine, 2008; Edge & Gold, 2014; Gosnell & Levine, 2009). For example, individuals may eat more to compensate for dietary neglect related to their former addictive lifestyles or use food as an alternative coping response. Unhealthy eating habits, particularly the ingestion of high sugar and fat foods in individuals with SUD, may contribute to weight gain by providing an alternative reward replacement for drugs (Billing & Ersche, 2015; Volkow, Wang, Fowler, Tomasi, & Baler, 2012). Weight gain in recovery from alcohol and substance use disorder has been documented in the literature. As such, targeting healthy lifestyles that include exercise and nutrition would be important adjunctive interventions in SUD recovery.

Gender and racial/ethnic differences have been reported in physical activity with Hispanics and non-Hispanic AA less physically active than non-Hispanic Caucasian (Dai et al., 2015). Such differences include reasons for exercise, motivation to initiate and maintain regular exercise, choice or type of exercise preferred, exercise expenditure and physiologic responses to exercise (Chalabaev, Sarrazin, Fontayne, Boiché, & Clément-Guillotin, 2013; Furnham, Badmin, & Sneade, 2002; Nomaguchi & Bianchi, 2004). Motivation may also be affected by racial/ethnic minority groups having limited access to athletic facilities or recreation centers, living in neighborhoods perceived as unsafe and time constraints (Saffer, Dave, Grossman, & Ann Leung, 2013; Saint Onge & Krueger, 2011). Finkenberg et al. 1994 found gender differences in personal incentives for exercise. Men were more oriented toward competitive activity while women were more likely to exercise for weight management and appearance (Finkenberg, Dinucci, McCune, & McCune, 1994). Abrantes et al. 2011 found gender differences in exercise preference with women preferring yoga, walking and exercise videos while men preferred running, sports and strength/ resistance training. Men were more likely to prefer doing exercise on their own while women preferred to have some professional guidance (Abrantes et al., 2011). In a recent study exploring adjunctive exercise for women enrolled in SUD treatment, women were asked about exercise preference and reasons for exercise. Women favored such exercises as dance, yoga, tai chi with music, and social interaction as factors that enable enjoyment and intent to continue exercise. Weight loss, aesthetics and health were the most frequently cited reasons for exercise (Hsieh, 2015). In a study exploring reasons for initiating methamphetamine use, women were five times more likely than men to report using for weight reduction (Brecht, Greenwell, & Anglin, 2007). Other areas of gender and racial/ethnic differences in exercise include time spent exercising, peak exercise capacity and engaging in vigorous exercise (Grzywacz & Marks, 2001; Nomaguchi & Bianchi, 2004; Yuehui Zhou, Min Zhao, Chenglin Zhou, & Rena Li, 2016). One study found that AA females were found to have lower resting metabolic rates and lower cardiorespiratory fitness than Caucasian (Lavie, Kuruvanka, Milani, Prasad, & Ventura, 2004; Shook et al., 2014). In a large representative sample from the National Health and Nutrition Examination Survey (NHANES), males spent more time per day engaging in moderate to vigorous exercise than females (average 30 min for males vs 18 min per day for females) (Loprinzi & Cardinal, 2012). More recently, results from the 2018 National Health Interview Survey found males aged 18 years and over had higher rates of meeting the

current federal physical activity guidelines than females (28.8% versus 20.1%, age adjusted) (CDC/NCHS, 2018; ODPHP, 2018). Non-Hispanic Caucasian (26.8%) were more likely to meet the guidelines than non-Hispanic AA (20.8%) and Hispanics (18.7%).

There is a lack of research exploring gender and racial/ethnic differences in response to exercise, which can subsequently impact motivation to exercise as well as continuation of exercise in recovery programs. This is particularly important since weight gain in recovery may be a relapse trigger for females. The primary aim of the current study is to explore gender and racial/ethnic differences in physiologic responses to an exercise or health education intervention implemented for individuals with stimulant use. This is a secondary analysis of the CTN Stimulant Reduction Intervention using Dose Exercise (STRIDE) study, a high intensity dosed exercise intervention (DEI) compared to a health education intervention (HEI) in patients enrolled in SUD treatment. The primary study outcome found no between group or group by gender differences in stimulant use. There were several between group racial/ethnic differences in stimulant use after adjusting for adherence. That is, in the DEI versus the HEI group there was a lower probability for stimulant use in AA compared to Hispanics. There was also a larger reduction in substance use days for Caucasians but not for AA and other race/ethnicities in the DEI compared to the HEI intervention (Sanchez et al., 2017). This current secondary analysis was designed to answer the following questions; (1) Are their gender and racial/ethnic differences across the two intervention groups in measures of physiologic response and stimulant withdrawal severity? (2) In the DEI group, are there gender differences in the number of sessions attended and adherence to the prescribed dose of exercise? Specifically, measures of Body Mass index (BMI), waist circumference (WC), heart rate (HR) and stimulant withdrawal severity will be explored to determine the potential impact of physiologic problems that may complicate recovery.

2. Methods

2.1 Study Participants

Participants (females $n = 121$ and males $n = 181$) were from the Stimulant Reduction Intervention using Dose Exercise (STRIDE) trial, a National Drug Abuse Treatment Clinical Trials Network study (CTN-0037). Full details about the protocol and main study results are described elsewhere (Trivedi et al., 2017; Trivedi et al., 2011). Briefly, recruitment occurred during residential treatment in nine geographically diverse community treatment programs in the US that had a 21- to 30-day residential length of stay and post-residential outpatient services. Eligible participants reported illicit stimulant drug use (e.g., cocaine, methamphetamine or amphetamine) in the 30 days prior to residential treatment program (RTP) entry and received medical clearance for exercise. Individuals with an opioid dependence diagnosis, general medical conditions that contraindicated exercise, and those with psychosis or other psychiatric conditions that posed a potential safety risk were excluded. The study was approved by all prospective site IRBs and participants provided informed consent prior to any study procedures.

2.2 Assessments

All measures utilized for the STRIDE trial were described in Trivedi et al., 2011 (Trivedi et al., 2011).

The Addiction Severity Index-Lite (ASI-Lite) assessed problems associated with drug use in seven domains: medical, employment, alcohol, drug, legal, family/social, and psychiatric. The ASI also provided lifetime years of primary stimulant use (cocaine, amphetamine, or methamphetamine). Baseline demographic variables collected from the ASI included age, race/ethnicity, employment status, and marital status (McLellan et al., 1992).

The Composite International Diagnostic Interview (CIDI), a structured diagnostic interview to evaluate the presence of DSM TR IV Axis I psychiatric disorders, was used to determine stimulant use disorders (cocaine only, cocaine and other stimulants, or other stimulants only) (Robins et al., 1988). The Mini International Neuropsychiatric Interview (MINI) measured DSM-IV psychiatric disorders, including major depression, dysthymia, mania, post-traumatic stress disorder (PTSD), panic disorder, social phobia, and obsessive compulsive disorder (OCD) (Sheehan et al., 1998).

Physiological Indices included height, weight, waist circumference and heart rate. Participant height was measured at baseline. Weight and waist circumference collected at baseline and monthly visits were used in this analysis. Body Mass index (BMI) is an approximate measure of body fat. It is calculated by weight in Kilograms (Kg) divided by height squared (in centimeters). The World Health Organization set cut off points for being overweight at $> 25 \text{ kg/m}^2$ and for obesity at $> 30 \text{ kg/m}^2$ (WHO, 2000, 2015). A BMI of 30 kg/m^2 is equivalent to approximately 35% body fat in young female adults and 25% in young adult males. A BMI between 25 and 30 kg/m^2 is considered overweight and normal BMI is lower than 25 kg/m^2 . The WHO has established cut off waist circumference points for both males and females at risk for metabolic disorders as $> 94 \text{ cm}$ (37 inches) for males and $> 80 \text{ cm}$ (31.5 inches) for females (WHO, 2011). At every exercise session, blood pressure was measured before, at 5 minutes and post exercise. Heart rate was obtained before and throughout the exercise session using a Polar RS400 Heart Rate Monitor.

The Stimulant Selective Severity Assessment (SSSA), based on the Cocaine Selective Severity Assessment (CSSA) measures self-reported stimulant withdrawal symptom severity for the past 24 hours (Kampman et al., 1998). The SSSA covers cocaine, methamphetamine, and other stimulants. Domains include carbohydrate craving, mood, appetite, sleep, energy, activity, anxiety, attention, pulse rate and substance craving. Participants indicate the frequency or intensity of their withdrawal experiences for 16 individual symptoms on a scale of 0 to 7, including, for example, anxiety (i.e., 0 usually doesn't feel anxious; 3–4 anxious half the time; and 7 anxious all the time) and irritability (i.e., 0 = most things are not irritating; 3–4 = many things are irritating; and 7 = mostly everything is irritating or upsetting). The maximum possible score is 112. Mulvaney et al., 1999 et al., found that individuals with scores above 24 were five times more likely to drop out of treatment and scores above 31 were three to four times less likely to achieve abstinence in the first month of treatment than those with scores below 24 and 31, respectively (Mulvaney, Alterman,

Boardman, & Kampman, 1999). The SSSA was collected at baseline and weekly throughout the study.

2.3 Procedure

Exercise in the lab was conducted individually and consisted of supervised walking or running on a treadmill three times a week in the exercise lab for the first 12 weeks. For the remaining 24 weeks supervised exercise sessions were conducted once weekly in the lab with the expectation that participants complete the other two unsupervised sessions on their own. Resting heart rate (HR) was measured at the beginning of each exercise session. Participants were titrated up to a prescribed dose of 12 Kcal/Kg/week (KKW) which is equivalent to 120–150 minutes of exercise a week or 30 minutes 4–5 times a week over the first 3 weeks and continued at this dose for the remaining weeks. The target intensity of the exercise was 70–85% of each participant's maximum heart rate (HR max) which was determined during the maximal exercise test that was conducted at baseline to medically clear participants to exercise. The HR max was also titrated to the targeted intensity over the first 3 weeks. The Health Education control Intervention consisted of therapist facilitated sessions three times a week for the first 12 weeks then weekly for the remaining 24 weeks. Participants were provided with educational items in the form of didactic presentations, readings, websites and audio/video recordings of common health related topics such as cardiovascular disease prevention and healthy eating habits. Participants in both groups wore a pedometer to monitor activity.

2.4 Statistical Analysis

This is a secondary analysis of the STRIDE trial which was designed to ascertain the value of exercise among individuals recovering from stimulant use disorders. The current statistical analyses explored gender and racial/ethnic differences on measures of BMI, waist circumference, heart rate and SSSA over time.

Demographic and SUD variables for males and females were compared using univariate analysis of variance for continuous variables and chi square for dichotomous variables. Previously reported, there were no differences in substance use outcomes by gender (Trivedi et al., 2017). Due to the group sizes, the race and ethnicity variables were collapsed in the analysis to non-Hispanic Caucasian, non-Hispanic African American (AA) and Other race/ethnicity (Other). The Other group was represented by Hispanic/Latinos (72%), Non-Hispanic Multiracial (19%) and Native Americans (9%). In the exercise group, gender differences were compared for mean session attendance; at home exercise and Kcal/Kg/Week expended using GLM univariate analysis of variance.

Data for each participant on BMI, waist circumference and heart rate were collected up to 36 weeks throughout the course of the study. Additionally, SSSA was conducted at each patient visit. The association between the outcomes with treatment group, race/ethnicity, gender and time (visit week) was evaluated using a series of linear mixed regression models (LMMs). Gender, time and other predictors such as race/ethnicity, age, treatment group, as well as stimulant severity indices (SSSA) which could modify the relationship of interest were added to each model. For all outcomes, fixed effects considered in each model included

treatment group, gender, race/ethnicity (Caucasian, AA, or Other), time, and the interactions between gender and time. We also consider a multiplicative effect of time and thus considered time squared in the models as well. Models also included random effects for participant and time to account for correlation between measures on the same participant over time. Different covariance structures, including compound symmetric, auto-regressive, and unstructured covariance were considered and the final model for each outcome was selected based on the model with the smallest Aikake's Information Criterion (AIC) though treatment assignment was retained in all models regardless of significance or impact on model fit. The outcomes, BMI, waist circumference, heart rate, and SSSA score (for all scores >0) were log transformed prior to model fitting in order to meet statistical assumptions and thus results from the models are interpreted as percent differences between groups being compared. Comparisons between groups were evaluated using linear contrasts from the LMMs and p-values were Bonferroni adjusted to account for multiple testing. All analyses were performed in SAS v. 9.4 (SAS Institute, Cary, NC).

Due to the large number of zero scores on the SSSA for patients collected over time, we used a zero-inflated log-normal mixed effects model to assess the association between SSSA with treatment, gender, race, and time. Zero-inflated log-normal mixed effects first model the probability that a participant's SSSA score is zero, and then conditions on the score being greater than zero to model the association between fixed effect with non-zero SSSA scores.

3. Results

3.1 Demographic

Demographic and physiologic variables are displayed in Table 1. The average age of participants was 39 ± 10.8 with females being significantly younger (35.7 ± 9.9) than males (41.2 ± 10.8). Males were more likely to be AA (50% vs 30% for females) and females were more likely to be Other (Hispanic/Latino 17% vs 6% for males). Most participants were either never married (53%) or divorced/separated/widowed (33%) with no gender differences in marital status. Males were more likely to be employed (39% vs 20% for females). At baseline, females had a higher BMI than males (28.7 vs 27.3 , $p < 0.05$, respectively). Baseline waist circumference, total SSSA scores and initial heart rate measure (prior to initiation of exercise) were not significantly different between genders. Table 2 displays average session attendance and adherence to the prescribed exercise dose of 12 KKW by gender across the 9- month study. Across the nine months males engaged in significantly more exercise sessions than females (45.1 ± 3.2 vs 32.7 ± 3.0 ; $p = .005$) and were more adherent to the prescribed exercise dose of 12 KKW (7.85 ± 2.1 KKW vs 6.75 ± 1.8 KKW; $p < .001$, respectively). Men also engaged in more at home exercise than females.

3.2 Body Mass Index (BMI)

There were significant associations between BMI and race, visit week, and the interaction between week and gender. Time in weeks had a significant multiplicative effect as the fixed effect for time squared was significant in the model. Specifically, AAs had a 7.74% higher BMI compared to Caucasian ($p = 0.002$) and Others (race/ethnicity) had a 13.1% higher

BMI relative to Caucasian ($p = 0.002$) after controlling for treatment group, gender and week (Table 3). Others (race/ethnicity) had a 4.96% higher BMI compared to AAs, however this difference was not significant after controlling for other factors. Thus, racial/ethnic groups were different at baseline, however gender differences over time were similar across racial/ethnic groups. There was a significant interaction between gender and visit week, therefore these factors were interpreted together. The estimated mean BMI over time by race and gender is shown in Figure 1. The percent difference in BMI between males and females increased over time with females having a higher BMI than males. Additionally, females on average showed an increase in BMI over time ($p < 0.001$) while male BMI showed no significant change over the course of the study.

3.3 Waist Circumference (WC)

There were significant associations between WC and race, visit week, and the interaction between week and gender. Time in weeks had a significant multiplicative effect as the fixed effect for time squared was significant in the model. Specifically, AAs had a 5.2% greater WC compared to Caucasians ($p < 0.004$) and Others (race/ethnicity) had 12.1% higher WC relative to Caucasians ($p < 0.001$) after controlling for gender and week (Table 4). Others (race/ethnicity) had a 6.54% higher WC compared to AA, however this difference was not significant after controlling for other factors. Thus, racial/ethnic groups were different at baseline, however gender differences over time were similar across racial/ethnic groups. There was a significant interaction between gender and visit week and the estimated mean WC over time by race and gender is shown in Figure 2. At baseline WC in females was similar relative to males but higher than males at 36 weeks. Over time females exhibited an increase in WC on average ($p < 0.001$) while males had a decrease in WC ($p = 0.025$).

3.4 Heart Rate (HR)

Heart rate was associated with week and the interaction between visit week and gender (Table 5). The estimated mean heart rate over time by gender is shown in Figure 3. On average, the heart rate for females was significantly higher at all time points relative to males though the difference at baseline was not significant. Males exhibited a decreased in heart rate over the course of the study while females exhibited an increase in heart rate.

3.5 Stimulant Selective Severity Assessment (SSSA)

The probability of a zero SSSA score was associated with race and visit week with gender and treatment retained in the model. Specifically, AA had significantly higher odds of a zero-score compared to Caucasians and Others (race/ethnicity) after controlling for treatment group, gender, and assessment time in weeks (OR (95% CI): AA vs. Caucasians, 2.72 (1.53, 4.82) and AA versus Others (race/ethnicity), 3.33 (1.32, 8.42), $p < 0.001$ for both). Additionally, a 12-week time increase was associated with a 51% increase in the odds of a zero-score controlling for other factors (OR (95% CI): 1.52 (1.39, 1.63, $p < 0.001$). Conditional on having a non-zero score, SSSA score was associated with race, visit week, and the interaction between gender and visit week. In contrast to the models of BMI, waist circumference, and heart rate, there was not a significant multiplicative effect of time on SSSA score and thus the model excluded time squared as a fixed effect. African Americans had a 38.4% lower SSSA score on average compared to Caucasians and a 36.9% lower

SSSA score compared to Others (race/ethnicity) ($p < 0.001$ for both) after controlling for treatment, gender and week (Table 6). There was a significant interaction between gender and week and the estimated mean SSSA score over time by race and gender is shown in Figure 4. The SSSA score was similar in males and females at baseline but males exhibited a significant decrease in SSSA score over time while females did not.

4. Discussion

Exercise has several health benefits that may be relevant to SUD recovery. In the current study there were several gender differences in exercise adherence and gender and race/ethnicity responses that may warrant consideration when designing exercise programs. Females enrolled in the exercise intervention were less likely than males to attend or engage in exercise sessions and adhere to the prescribed exercise dose throughout the study. The target dose for the exercise intervention was 12KKW which is equivalent to current public health recommendations. Energy expenditure for females in the current study averaged 6.75 KKW versus 7.85 KKW for the males. Individuals who engage in more vigorous exercise would attain the target KKW dose in less time than those who exercise at a moderate level. Several studies have found that females spend less time exercising than males, are less likely to engage in vigorous exercise and have a lower peak exercise capacity (Grzywacz & Marks, 2001; Nomaguchi & Bianchi, 2004). Given the nature of the specific exercise and level of prescribed intensity in the current study, females may have been less interested in or able to complete the prescribed exercise. Females may also have more barriers to exercise such as childcare and transportation or may prefer another type of exercise that has more social engagement. In the current study, a higher percentage of males compared to females reported no barriers to exercise with females reporting more transportation, emotional and injury barriers (Killeen, 2015).

Females in the current study on average gained more weight across time versus males who maintained or slightly lost weight. There were also differences in BMI among the three racial/ethnic groups with AA and Other race/ethnicities having higher baseline BMIs than Caucasian, although changes in BMI throughout the study were similar across the racial/ethnic groups. Higher rates of obesity in AA and Hispanic females compared to Caucasian females have been reported (Hales et al., 2018b; Flegal et al., 2016; Moore-Greene, 2012). In the current study, approximately 72 % of individuals in the Other race/ethnicity group were Hispanic and 78% of the females in the Other race/ethnicity group were Hispanic. Donnelly and colleagues failed to find weight reduction in sedentary, overweight females compare to males randomized to a 16-month supervised, moderate intensity exercise intervention. Despite no gender differences in session attendance, caloric intake or exercise intensity, males achieved a higher energy expenditure (6.7 Kcal/Kg) and weight loss (5.2 Kg) than females (5.4 Kcal/Kg and 0.06 Kg weight gain) (Donnelly et al., 2003). Females may need a higher negative energy balance (energy expenditure > caloric intake) than males to achieve weight loss or prevention of weight gain. Melanson et al., 2013 suggest that compensatory behaviors such as increasing caloric intake and reducing non-exercise activity (i.e. physical activities other than volitional exercise such as normal activities of daily life) may counteract weight reduction associated with exercise (Melanson, Keadle, Donnelly, Braun, & King, 2013). It is possible that females may have reduced their non-exercise

physical activity expenditure thereby negating weight reduction associated with prescribed exercise. However, the literature on measuring non-exercise energy expenditure associated with prescribed exercise is limited (Ostendorf et al., 2018; Washburn et al., 2014). There is a developing area of research exploring the food/drug reward areas in the brain, suggesting that highly palatable foods, particularly fat and sugar, may stimulate similar brain reward pathways in the absence of drugs (Smith & Robbins, 2013; Volkow et al., 2012). In one large study of females with stimulant use disorder and either full or subthreshold PTSD enrolled in community SUD treatment, 30% reported one or more binge eating episodes in the last 28 days (Cohen et al., 2010). Females may be more predisposed to compensating with food in the absence of drugs. It would be important to address dietary habits and eating patterns when helping females develop healthy lifestyles in recovery. Females may also require longer durations of exercise and greater exercise intensity in addition to greater reduction in caloric intake to achieve similar benefits as males. Unlike in the Donnelly study, exercise attendance in the current study was lower for females. In the latter 6 months of the study (month 3 to month 9), participants attended one weekly supervised exercise session in the study lab and were expected to engage in and record home exercise twice weekly (unsupervised outside of study lab). Females in the current study only reported half the number of expected home exercise sessions than males (12.5% vs 23%, respectively).

Because females are more likely to exercise in social environments and/or with professional guidance (Abrantes et al., 2011), it is possible that the female participants had a high level of reliance on supervised exercise and less motivated to exercise on their own. It is also possible that females may be more motivated to engage in exercise if they experience early weight control benefits. A recent study with women enrolled in a 12-week modest intensity aerobic exercise program found weight loss at 4 weeks was predictive of weight loss at 12 weeks (Sawyer et al., 2015). However, females in the current study experienced early weight gain which could adversely affect subsequent motivation. In another study, women enrolled in a SUD rehabilitation program were given a questionnaire on exercise preferences and motivations. Women favored such exercises as dance, yoga, tai chi with music, and activities with social interaction that enable enjoyment and intent to continue exercise (Hsieh 2015). A group exercise with more social involvement might better motivate females to engage in exercise.

In general, SSSA scores were in the lower severity range for both males and females. Across time, males had a reduction in SSSA scores while SSSA scores in females were largely unchanged. Although exercise has been associated with improvements in depression, anxiety and craving, females may experience other aspects of stimulant withdrawal such as increased appetite, carbohydrate craving, low energy and anhedonia which may interfere with exercise engagement and/or maintenance. Alternatively, the level of exercise performed by females in the current study may not have been enough to effect stimulant withdrawal severity.

Higher BMIs and WC seen in the current study can put females at greater risk for medical problems with high morbidity and mortality rates. Although there were racial/ethnic difference in BMI and WC for females at baseline, weight gain and increase in WC were similar in all racial ethnic groups across time. Recent data show higher obesity rates in non-

Hispanic AA and Hispanics than in non-Hispanic Caucasian (Hales et al., 2018b). Early life adversity and lower socioeconomic status have been more strongly associated with higher BMI in AA than Caucasian females (Curtis, Fuller-Rowell, Doan, Zgierska, & Ryff, 2016). Proposed mechanisms include increased physiologic vulnerability to the effects of stress and fewer supportive resources available for AA youth.

4.1 Limitations

There are several limitations to the current study. As caloric intake was not monitored, we are unable to determine if weight gain and increase in WC can be attributed to an increase in caloric intake. Although all participants wore a pedometer to assure the control group was not engaging in exercise beyond routine daily activity, changes in non-exercise physical activity were not monitored. As weight and body appearance was not a target outcome, it is not known if females were concerned about their weight and body shape. Body composition was not measured so weight gain does not represent accurate changes in body fat or muscle mass. An increase in muscle mass may account for some weight gain in individuals who exercise regularly, however, it is unlikely to be the cause of weight gain as females in the current study were only exercising at half of the prescribed dose and there were no treatment group differences in BMI and WC. Future studies should include body composition indices, monitor caloric intake and measure whether body appearance is an important issue for females.

4.2 Conclusion

In conclusion, weight gain in females may be attributed to lower levels of exercise (less time exercising and less adherence to prescribed dose, less vigorous exercise intensity), decrease in non-exercise physical activity and/or increase in caloric intake. Females with less intense exercise (i.e. walking) may take longer periods of time to meet their weekly adherence prescription. Time may be an additional barrier to exercise for females. Exercise can increase appetite and females may be eating more and thus, becoming more frustrated that exercise is not “working” for weight reduction. Females in SUD recovery are more sensitive to weight gain and body image (Killeen, Brewerton, Campbell, Cohen, & Hien, 2015). Adjunctive dietary counseling may improve weight gain in both males and females. This could include determining the energy expenditure necessary to exceed caloric intake in order to create a negative energy balance required for weight loss or weight maintenance. Programs may want to offer different types of exercise options for males and females. The exercise implemented in the current study may have been more acceptable to males and certain racial/ethnic groups. A group exercise such as aerobics or dance may increase motivation to sustain exercise engagement for females.

Addressing gender and racial/ethnicity specific barriers to engaging in exercise may improve adherence to exercise interventions. Providing transportation, more stretching/warming up prior to exercise, exercise involving social interaction, and a less intense level of exercise for injury prevention may address some of the specific barriers that females experience. Unintended weight gain may put females at risk for relapse and significant medical problems associated with obesity. A supportive individualized health plan that includes

exercise and nutrition counseling can be a valuable part of a recovery program, particularly for females.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Exercise is increasingly being incorporated into SUD recovery programs.

Although substance use outcomes are mixed, other responses to exercise are explored.

Gender differences indicate that females demonstrate an increase in weight and waist circumference across time.

Gender specific exercise programs are indicated to reduce disparities in exercise health benefits.

Figure 1:
BMI over time by gender and race determined from the LMM model

Figure 2:
Waist Circumference over time by gender and race from the LMM model

Figure 3:
Heart rate over time by gender from the LMM model

Figure 4: Stimulant Selective Severity Assessment score conditional on SSSA score >0 over time by gender and race/ethnicity from the LMM model

Table 1**Baseline Demographics and Physiologic Indices by Gender**

Baseline Variable	All N = 302	Male N = 181	Female N = 121	F	p-value
Age Mean (SD)	38.97 (10.8)	41.17 (10.8)	35.67 (9.9)	20.0	0.000
Race/Ethnicity N (%)					
Cau/Non-Hispanic	131 (43%)	73 (40%)	58 (48%)	2.8	0.094
AA/Non-Hispanic	128 (42%)	91 (50%)	36 (30%)	14.6	0.001
Hispanic/Latino	31 (10%)	10 (6%)	21 (17%)	11	0.001
Other/Not Hispanic	12 (4%)	7 (4%)	6 (5%)	0.5	0.474
Employed N (%)	95 (31%)	71 (39%)	24 (20%)	12.6	0.000
Marital Status N (%)				2.6	0.27
Married	40 (13%)	23 (13%)	17 (14%)		
Sep/Div/Wid	101 (33%)	67 (37%)	34 (28%)		
Never Married	161 (53%)	91 (50%)	70 (57%)		
Body Mass Index					
(Kg/m ²), mean (SD)	27.85 (5.7)	27.28 (4.8)	28.70 (6.8)	4.55	0.034 *
Cau	26.78 (5.7)	26.2 (4.3)	27.5 (7.1)	6.47	0.002 **
AA	28.14 (5.2)	27.7 (4.9)	29.2 (5.8)		
Other	30.25 (6.5)	29.6 (5.6)	30.7 (7)		
Waist Circumference					
(WC) in inches	36.78 (5.6)	36.85 (5.0)	36.69 (6.4)	.058	0.81
Cau	35.6 (5.1)	35.9 (4.1)	35.1 (6.2)	19.8	.05 **
AA	37.2 (5.3)	37.3 (5.3)	37 (5.4)		
Other	39.3 (7.0)	38.7 (6.8)	39.6 (7.3)		
Heart Rate (N = 152)	77.68 (10.5)	76.48 (10.3)	79.37 (10.7)	2.81	.096
SSSA Total Score	16.57 (14.8)	15.45 (14.0)	18.24 (15.9)	.824	0.109
Cau	20.9 (16)	20.4 (15.3)	21.5 (16.8)	2.66	0.001 **
AA	11.5 (11.3)	11.1 (11.1)	12.3 (12)		
Other	18.7 (16)	17.8 (15.3)	19.2 (16.6)		

Cau = Caucasian ; AA = African American

* significant for gender;

** significant for race

Table 2.

Exercise session attendance and adherence by gender (SD)

Outcome	Male N = 89	Female N = 63	t	X ²	df	p value
Average exercise sessions over 9 months *	45.1 (30.8)	32.7 (23.6)	2.8		149	.005
% exercise sessions at home during weeks 13–36	11 (23%)	6 (12.5%)		96.1	1	.001
Average Kcal/Kg/Week over 9 months **	7.85 (2.1)	6.75 (1.8)	3.8		150	.001

* Out of possible 60 supervised sessions and 48 home sessions

** Prescribed dose 12Kcal/Kg/Week

Table 3:

Percent difference in BMI by participant characteristics estimated from a linear mixed effects model of BMI.

Characteristic	% Difference (95% CI)	P
Treatment Group		
Exercise vs. Health Education	0.86 (−3.44, 5.35)	0.701
Race		
AA vs. Caucasian	7.74 (2.82, 12.9)	0.002
Other vs. Caucasian	13.1 (5.26, 21.5)	<0.001
Other vs. AA	4.96 (−2.47, 12.9)	0.197
Gender x Time		0.001
Female vs. Male at baseline	3.33 (−1.33, 8.22)	0.165
Female vs. Male at visit 24	4.86 (0.17, 9.77)	0.043
Female vs. Male at visit 48	6.41 (1.62, 11.4)	0.009
Female vs. Male at visit 60	7.98 (3.03, 13.2)	0.002

Covariates in model include gender, time, race/ethnicity, age, treatment group, stimulant severity

Table 4:

Percent difference in waist circumference in inches by participant characteristics estimated from a linear mixed effects model of Waist Circumference.

Characteristic	% Difference (95% CI)	P
Treatment Group		
Exercise vs. Health Education	1.47 (−1.73, 4.78)	0.373
Race		
AA vs. Caucasian	5.20 (1.63, 8.89)	0.004
Other vs. Caucasian	12.1 (6.32, 18.2)	<0.001
Other vs. AA	6.54 (0.94, 12.5)	0.022
Gender x Time		0.001
Female vs. Male at baseline	−1.66 (−4.95, 1.75)	0.832
Female vs. Male at week 12	−0.47 (−3.77, 2.94)	0.607
Female vs. Male at week 24	0.73 (−2.62, 4.20)	0.336
Female vs. Male at week 36	1.95 (−1.51, 5.53)	0.274

Covariates in model include gender, time, race/ethnicity, age, treatment group, stimulant severity

Table 5:

Percent difference in heart rate by participant characteristic estimated from a linear mixed effects model of heart rate.

Characteristic	% Difference (95% CI)	<i>P</i>
Treatment Group		
Exercise vs. Health Education	−1.70 (−7.08, 3.99)	0.551
Gender x Time		0.001
Female vs. Male at baseline	3.39 (−0.41, 7.33)	0.083
Female vs. Male at week 12	5.29 (1.45, 9.27)	0.007
Female vs. Male at week 24	7.22 (3.19, 11.4)	<0.001
Female vs. Male at week 36	9.20 (4.81, 13.8)	<0.001

Table 6:

Odds ratio for the probability SSSA score is 0 (from the logistic portion of the model)

Characteristic	OR (95% CI)	p
Treatment		
Exercise vs. Health Education	1.15 (0.68, 1.97)	0.603
Race		
AA vs. Caucasian	2.72 (1.53, 4.82)	<0.001
AA vs. Other	3.33 (1.32, 8.42)	<0.001
Other vs. Caucasian	0.82 (0.33, 2.05)	0.666
Gender		
Female vs. Male	0.78 (0.44, 1.37)	0.381
Time		
12 Week increase	1.51 (1.39, 1.63)	<0.001
Percent difference given SSSA > 0 (from the log-normal portion of the model)		
Characteristic	% Difference (95% CI)	P
Treatment		
Exercise vs. Health Education	-4.07 (-17.5, 11.5)	0.589
Race		
AA vs. Caucasian	-38.4 (-47.8, -27.6)	<0.001
AA vs. Other	-36.9 (-51.2, -13.7)	<0.001
Other vs. Caucasian	-2.83 (-23.9, 25.3)	0.8548
Gender x Time		
Female vs. Male at baseline	0.75 (-14.8, 19.2)	0.931
Female vs. Male at week 12	11.8 (-4.54, 30.9)	0.168
Female vs. Male at week 24	24.0 (5.40, 45.9)	0.010
Female vs. Male at week 36	37.6 (14.8, 64.8)	<0.001