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Exercise Outcomes in Prevalent Users of Stimulant Medications

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Abstract

Background—To compare users of stimulant medications with matched nonusers on exercise outcomes during a maximal treadmill exercise test.

Methods—A cross-sectional study of a community-based cohort comparing propensity-score-matched stimulant medication users (n=245) and nonusers (n=735) who underwent a maximal treadmill exercise test in the Cooper Center Longitudinal Study cohort from January 1, 1995 to December 31, 2013. Main Outcomes were peak systolic blood pressure (SBP), average rise in SBP, peak heart rate (HR), and estimated VO₂max during exercise. A linear mixed model analysis was used to evaluate the effect of stimulant exposure on each of the exercise outcomes. In a

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Conflict of Interest: ANW has previously consulted as an expert witness in a single civil case. All other authors report no conflicts of interest.

Contributors: ANW conceived the study and PAN, CEB, ESB, and LFD helped with its development. ANW, PAN, CEB, and LFD had full access to all of the data in the study. CEB and LFD take responsibility for the integrity of the data. ANW and PAN conducted the data analysis and take responsibility for its accuracy. ANW and LFD are the guarantors. ANW and PAN designed the study. CEB and LFD acquired the data. ANW, PAN, and WV analyzed and interpreted the data. ANW and PAN drafted the manuscript. ANW, PAN, CEB, WV, BA, ESB, EMM, EAH, and LFD critically revised the manuscript. All authors have approved the final version of the manuscript submitted for publication.

sensitivity analysis, users were compared against nonusers for risk of chronotropic incompetence. Analyses were adjusted for relevant covariates and multiple testing.

Results—Peak HR during exercise was significantly lower in stimulant medication users (least square mean estimate 170.2 beats/minute) compared to nonusers (174.4 beats/minute; $p<0.0001$). Moreover, stimulant medication users had an increased risk of chronotropic incompetence compared to nonusers (adjusted odds ratio 3.28, 95% confidence interval 1.70 to 6.34, $p=0.0008$). No significant differences were observed in the outcomes of peak SBP, average SBP rise, and estimated $VO_2\text{max}$ between matched groups.

Conclusions—Stimulant medication use was associated with a significant decrease in peak HR and an increased risk of chronotropic incompetence. Further investigation is required to understand the clinical significance of chronotropic incompetence in stimulant medication users. Concerns that stimulant medication use may increase peak SBP and average SBP during exercise were not supported by this study.

1 INTRODUCTION

Prescription stimulant use is increasing in the United States, particularly among adults (Turning, 2014). Concern has been raised about the cardiovascular effects of stimulant drugs in adults (Nissen, 2006; Antel et al., 2014). Short-term randomized controlled trials (RCTs) of adults treated with stimulants have shown increased resting blood pressure and heart rate (HR) (Mick et al., 2013). This has provoked interest because of epidemiological studies showing that increases in these parameters are associated with cardiovascular morbidity and mortality (Psaty et al., 2001). The most ambitious study evaluating the association of stimulant use (median use 4 months) and serious cardiovascular events in adults did not show increased risk (Habel et al., 2011). The long-term effects of stimulants on blood pressure and HR (Vitiello et al., 2012; Bejerot et al., 2010) are difficult to study due to expense and ethical challenges.

Perturbations in blood pressure and HR during exercise have been linked to cardiovascular mortality and morbidity (Allison et al., 1999; Kurl et al., 2001; Lauer et al., 1996). Acute administration of medications that increase catecholamines has been shown to cause elevations in peak blood pressure and HR during exercise (Roelands et al., 2008; Swart et al., 2009; Watson et al., 2005; Roelands et al., 2012). However, published guidance for medical providers and patients on the impact of prevalent/chronic stimulant use on exercise is lacking. Thus, we conducted a study to compare prevalent stimulant medication users to matched nonusers undergoing a maximal treadmill test for differences in peak systolic blood pressure (SBP), average rise in SBP during exercise, peak HR, and aerobic exercise capacity (estimated $VO_2\text{max}$).

2 METHODS

2.1 Study Design and Study Population

This was a propensity-score matched cross-sectional analysis of persons enrolled in the Cooper Center Longitudinal Study (CCLS) cohort from 1995 to 2013, comparing stimulant medication users to nonusers. The CCLS is a cohort of self/physician/employer-referred

persons who undergo a standardized preventative medical examination and maximal treadmill exercise testing at the Cooper Clinic in Dallas, Texas. Participants in the study were generally non-Hispanic white (>90%), well-educated, and had access to preventative healthcare.

Participants were excluded as per criteria in Figure 1. Participants reporting a history of ADHD without use of a stimulant medication were excluded due to concerns about unreported stimulant use (misclassification) and confounding by contraindication. Over-the-counter drugs or supplements possibly containing ephedra included Dexatrim, Herbalean, Lean-r-gy, Lipodrene, Hydroxycut, Metabolife, Thermolift, Xenadrine, Yellowjacket, and Zytotherm. After exclusions, 19,744 participants were available for propensity score matching.

The study was 1) carried out in accordance with the latest version of the Declaration of Helsinki, 2) annually reviewed by the Institutional Review Board of the Cooper Institute, and 3) obtained informed consent from all participants.

2.2 Procedures and Measures

2.2.1 Exercise testing—Each participant underwent a previously described maximal treadmill exercise test (Willis et al., 2011). Cardiorespiratory fitness was estimated with total time on the treadmill using a modified Balke protocol. Briefly, the treadmill test began with no grade. At minute 2, the grade increased to 2% and increased 1% per minute until minute 25. The treadmill speed began at 3.3 miles/hour and remained so until minute 25. The speed then increased by 0.2 miles/hour each minute until the test was terminated by the physician for medical reasons or when the participant reached volitional fatigue. Participants were encouraged to give a maximal effort.

2.2.2 Stimulant exposure—Prior to exercise testing, participants reported all current medications. Participants reporting use of a stimulant medication were classified as stimulant users (primary definition, n=245; Appendix, Table A1). A secondary definition of stimulant medication use included only participants taking an amphetamine- or methylphenidate-type (AMP/MPH) stimulant (n=203) and was used in a sensitivity analysis. All other participants who did not report stimulant use were classified as nonusers (n=19,499). Thus, the independent variable was a binary indicator operationalized as “users” or “nonusers” (reference group) of stimulants. Dosage and duration of use of medications were not available. Participants were instructed to continue taking all prescribed medications prior to exercise testing.

2.2.3 Outcome variables—The outcome measures were peak SBP, average rise in SBP, peak HR, and VO₂max measured during the maximal treadmill exercise test. SBP was measured using an automated blood pressure cuff at 5 minute intervals during the exercise testing, while HR was recorded every minute from an electrocardiogram monitor. Peak SBP was defined as the maximum SBP (millimeters of mercury [mmHg]) reading during the exercise test. Average rise in SBP was defined as the average rise in the SBP per minute of exercise time and was operationalized as resting SBP subtracted from the peak SBP divided by total minutes elapsed during exercise (mmHg/minute) (Kurl et al., 2001). Average rise in

SBP was log transformed to obtain a more normal distribution. Peak HR was defined as the maximum HR attained during exercise (beats/minute). Estimated VO₂max was defined as the maximum oxygen consumption during exercise and was operationalized via the final speed and grade of the treadmill exercise test using the American College of Sports Medicine calculation equation (mL/kg/min) (Thompson et al., 2009).

2.2.4 Covariates—Covariates were selected *a priori*. The 18 baseline covariates listed in Table 1 were used for propensity score matching and were also included in all of the analytic mixed models. Self-report of current alcohol use, current smoking, family history of heart disease, history of diabetes mellitus, history of high cholesterol, current use of lipid-lowering medication, and history of hypertension were binary indicators (yes/no). Participants were instructed to indicate their race/ethnicity by selecting just one of the following: Caucasian, African American, Hispanic, Asian, American Indian, or other. Because of the small percentage of participants who did not self-identify as non-Hispanic white, they were combined into one category. Self-report of physical activity (MET-min) was log transformed to obtain a more normal distribution (because of positive skewness).

2.3 Propensity-Score Matching

A propensity score-matched sample of stimulant users and nonusers was created using the 18 observed covariates (Table 1). The propensity score, defined as a participant's probability of being exposed to stimulant medications conditional on the 18 observed covariates, was used to balance the covariates among users and nonusers, and thus mitigate potential selection bias on those covariates (D'Agostino, Jr., 1998). Each participant's propensity score was estimated using a logistic regression model (AUC=0.748, SE=0.017, 95%CI=0.742 to 0.755), with exposure to stimulant medication as the outcome, based on the 18 observed covariates. Next, each stimulant user was matched to three nonusers with respect to their propensity scores using the GREEDY matching algorithm procedure (GMATCH procedure) (Bergstralh & Kosanke, 2003), via nearest-number matching with a propensity score caliper of ± 0.05 with no replacement. The average observed absolute user/nonuser propensity score difference (distance) was 0.0003 (SD=0.002). Stimulant medication users were compared to the matched and unmatched nonusers for all 18 baseline covariates (Table 1). Histograms of the observed propensity score distribution in the matched stimulant users and nonusers and pre-matched nonusers demonstrate the tight matching that was achieved (Figure 2). The same matching procedure was employed for the secondary definition of stimulant use (AMP/MPH).

2.4 Statistical Analysis

The primary data analysis was a linear mixed model analysis designed to evaluate the effect of stimulant medication exposure on each of the outcomes during the exercise test in the propensity score-matched sample. The respective mixed models were conducted with and without the 18 covariates included in the model. Restricted maximum likelihood estimation, Type 3 tests of fixed effects, and generalized least squares were used, with the Kenward-Roger correction applied to the compound symmetry covariance structure. The correlation structure of the matched participants was accounted for in the mixed model analysis by treating each block of matched participants as a random effect.

2.4.1 Sensitivity analysis—In a mixed model analysis similar to that described above for each outcome, covariates found to have statistical significance in the primary covariate-adjusted mixed models were then tested in subsequent (*post hoc*) mixed models for interaction with stimulant medication exposure status. Finally, to further understand the effect of stimulant medication exposure on peak HR, we implemented a *post hoc* sensitivity analysis designed to examine the relationship between chronotropic incompetence (inappropriately low HR in response to activity demands) and stimulant exposure. In this sensitivity analysis, chronotropic incompetence was a binary outcome (present/absent). The presence of chronotropic incompetence was operationalized as less than 80% Heart Rate Reserve (Azarbal et al., 2004). Age-predicted maximum HR was calculated using the Tanaka formula: $208 - (0.7 \times \text{age})$ (Tanaka et al., 2001). Logistic regression within a Generalized Linear Mixed Model (GLMM) context, while accounting for each block of matched participants as a random effect, was used to estimate the odds of chronotropic incompetence from stimulant exposure with and without adjusting for the 18 covariates in the model.

2.4.2 Testing for multicollinearity—To ascertain the presence of any multicollinearity in our linear regression models, we examined the variance inflation factor for each of the 18 covariates in each model. The estimated variance inflation factors for the covariates ranged from 1.01 to 2.19, suggesting that multicollinearity was not present or problematic.

All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC). The propensity scores were estimated using the PROC LOGISTIC procedure in SAS. The GMATCH computational SAS macro was used to implement the propensity score matching (Bergstralh & Kosanke, 2003). Finally, the PROC GLIMMIX procedure in SAS was used for the mixed model analyses. The level of significance for all tests was set at $\alpha = .05$ (two-tailed). The False Discovery Rate (FDR) procedure was implemented to control for false-positives over the sets of multiple tests of the main effects for stimulant exposure on each outcome.

3 RESULTS

3.1 Characteristics of Stimulant Users and Nonusers in the Propensity Score-Matched Sample

Prior to propensity score matching, stimulant medication users and nonusers differed across many of the 18 observed covariates (Table 1). Compared to nonusers, stimulant medication users were more likely to be younger, female, report current smoking, report no family history of heart disease, to have lower resting blood pressure and a higher resting HR, and to have undergone the maximal treadmill exercise test in more recent years. In contrast, after the propensity score matching procedure, matched users and nonusers were very similar across the 18 observed covariates (Figure 2).

3.2 Exercise Outcomes and Stimulant Exposure

The primary linear mixed model analyses adjusted for the 18 covariates revealed that there were no significant differences in the propensity score-matched sample between stimulant

medication users and nonusers on peak SBP, log of average SBP rise, and VO₂max (Table 2). However, while controlling for the 18 covariates, we found a significant main effect of stimulant medication use on peak HR [users vs. nonusers; $F(1, 724.3) = 24.19, p < 0.0001$]. The pattern of the adjusted least squares means showed that peak HR was significantly lower for users than for nonusers [170.2 (SE=2.02) vs. 174.4 (SE=1.92), raw $p < 0.0001$, FDR-adjusted $p = 0.0004$; Table 2].

Linear mixed models of each exercise outcome were repeated *without* adjusting for the 18 covariates in the model and showed the same pattern of results as those described above for the covariate-adjusted mixed model (Table 3).

Analyses where the secondary definition of stimulant use was employed (i.e. only participants taking AMP/MPH stimulants) showed the same pattern of results as the mixed models from the primary definition of stimulant use. Stimulant medication use compared to non-use was not associated with a significant difference in peak SBP, log of average SBP rise, and VO₂max, but was associated with significantly decreased peak HR ($p < 0.0001$; results not shown).

3.3 Sensitivity Analyses for Exercise Outcomes and Stimulant Exposure

As a sensitivity analysis, covariates found to have statistical significance in the primary covariate-adjusted mixed models were tested in subsequent (*post hoc*) mixed models for interaction with exposure status (stimulant users vs. nonusers). We found no significant interaction effects on any of the four exercise outcomes (results not reported). Finally, to further understand the effect of stimulant exposure on peak HR, we implemented a *post hoc* sensitivity analysis examining the relationship between chronotropic incompetence (as a binary outcome) and stimulant exposure in the propensity score-matched sample. Among stimulant users, 22 of 245 had chronotropic incompetence. Logistic regression (GLMM) without adjusting for the 18 covariates in the model revealed that stimulant use had 2.32 times the predicted odds of chronotropic incompetence than nonuse [odds ratio = 2.32, 95% CI = 1.30 to 4.12, $F(1, 773.9) = 8.21$, raw $p = 0.004$, FDR-adjusted $p = 0.004$]. Similarly, after adjustment for the 18 covariates in the model, the predicted odds of chronotropic incompetence with stimulant use persisted [adjusted odds ratio = 3.28, 95% CI = 1.70 to 6.34, $F(1, 867.1) = 12.62$, raw $p = 0.0004$, FDR-adjusted $p = 0.0008$].

4 DISCUSSION

To our knowledge, this is the first study to examine stimulant medication use and maximal exercise test outcomes in a large community sample. In this cross-sectional study, stimulant medication users unexpectedly had a significantly lower peak HR than matched nonusers, despite non-differential performance (VO₂max) between the groups. A *post hoc* analysis further demonstrated a significantly increased risk of chronotropic incompetence during exercise testing among users compared to matched nonusers. There was no significant difference in the outcomes of peak SBP, average SBP rise, and estimated VO₂max comparing users to matched nonusers. In contrast, previous exercise studies have shown increases in exercise performance and HR associated with *acute* use of methylphenidate and bupropion (which also blocks dopamine and norepinephrine reuptake) as compared to

placebo (Roelands et al., 2008; Swart et al., 2009; Watson et al., 2005; Roelands et al., 2012).

Chronotropic incompetence is defined as an inappropriately low HR in response to activity demands. It is associated with cardiovascular disease and heart failure, as well as exercise intolerance and lower quality of life (Brubaker & Kitzman, 2011). It is an independent predictor of serious cardiovascular events and mortality (Lauer et al., 1996). Drugs such as amiodarone, beta blockers, calcium channel blockers, and digitalis may induce or confound determination of chronotropic incompetence (Brubaker & Kitzman, 2011). That a stimulant might cause chronotropic incompetence was suggested by a study of habitual cocaine smokers who were found to have a lower peak HR compared to matched controls (Marques-Magallanes et al., 1997). The results of our study, if confirmed, suggest that stimulant medications may do the same.

Both heart failure and beta blocker use are strongly associated with a higher prevalence of chronotropic incompetence (Cullington et al., 2013). However, stimulants are likely to induce chronotropic incompetence by a different mechanism than beta blockers since resting heart rate is reduced by beta blockers but not by stimulants. By what mechanism could stimulant medications, like heart failure, cause chronotropic incompetence? Both acute stimulant use and heart failure (due to sympathetic overactivity) lead to elevated circulating levels of norepinephrine (Volkow et al., 2003; Cohn et al., 1984). In turn, the diminished chronotropic response seen in heart failure patients has been linked to post-synaptic beta-adrenergic receptor desensitization (Colucci et al., 1989). Thus, the common pathway for both chronic stimulant medication use and heart failure may be elevated norepinephrine leading to receptor desensitization and finally an increased risk of chronotropic incompetence.

It is premature to make any conclusions about the clinical significance of the observed association between stimulant medication use and chronotropic incompetence. If the results of this observational study are confirmed, additional studies are required to test whether stimulant-associated chronotropic incompetence is associated with mortality and serious cardiovascular events. Because the clinical significance of chronotropic incompetence among stimulant medications users is unknown, we do not currently recommend screening for it in otherwise healthy patients. However, based on the current study alone, it may be prudent for clinicians to add stimulants to the list of medications that can induce or confound the finding of chronotropic incompetence. In the interim, this study suggests that researchers consider that the chronic effects of stimulants may be very different than the acute effects.

There are other potential explanations for the observation that peak HR was reduced among stimulant medication users. Unmeasured confounders of stimulant use and heart rate could have accounted for our observations. However, the propensity score matching used in the current study gives us confidence that the groups were similar with regard to the 18 observed covariates, including baseline resting HR and level of physical activity prior to maximal exercise testing. A potential confounder that could not be measured was motivation during exercise testing. However, we note that stimulant users and nonusers demonstrated the same amount of aerobic capacity, as evidenced by the equivalent estimated $\text{VO}_{2\text{max}}$.

The study findings were unlikely to be confounded by other drugs that can induce chronotropic competence because all participants taking a drug for hypertension (e.g. beta blockers and calcium channel blockers) were excluded. Confounding by contraindication and survivor bias might be an additional explanation for decreased peak HR among prevalent users of stimulant medications. That is, persons likely to experience adverse events may not have ever been prescribed stimulants, and those that were and experienced adverse events (e.g. palpitations, tachycardia) may have stopped taking the medication and be classified as nonusers. Questions about heterogeneity of indications for stimulant use in the study population as a source of confounding are muted by the secondary analyses where stimulant use was limited to just AMP/MPH. Those results mirrored the primary finding. Also, stimulant medication users may have fundamentally different physiological characteristics that precede stimulant use, as stimulant treatment-naïve children with ADHD have been shown to have a blunted catecholamine response to exercise despite performing the same amount of work as controls (Wigal et al., 2003). Lastly, any theorized inotropic effect of stimulant use leading to a lower peak HR would be unlikely due to the necessity of a selective inotropic effect in the absence of a chronotropic effect, given that baseline resting HR was the same among stimulant users and nonusers.

If stimulants had increased peak SBP and average SBP in the study or led to lower cardiorespiratory fitness, this could have caused concern about an associated risk of serious cardiovascular events (Allison et al., 1999; Kurl et al., 2001; Carnethon et al., 2003). However, these other safety signals—peak SBP, average SBP rise, and VO_2max —did not differ between stimulant medication users and nonusers.

Finally, this study of prevalent stimulant medication use adds to the growing body of evidence of a more nuanced and complex relationship between stimulation medication use and hemodynamic parameters. Based on consistent findings in short-term efficacy RCTs, clinicians generally think of stimulants causing elevations in SBP and HR (Mick et al., 2013). However, two long-term non-controlled studies have shown no increase in blood pressure paired with an increase in resting HR (Vitiello et al., 2012; Bejerot et al., 2010). A third study contradicted this in finding significantly increased resting SBP and unchanged resting HR over 24 months (Wilens et al., 2005). Even with acute use, the effects of stimulants may be differential among users. Our prior study showed an inverse relationship between resting blood pressure and stimulant-induced increases in resting blood pressure (Westover et al., 2013), suggesting that baseline activity of the sympathetic nervous system prior to stimulant use may have an impact on its effect. Similarly, the current study if confirmed suggests that over time prevalent use of stimulants may itself modulate the autonomic nervous system.

There are limitations to the current study. Dosing of stimulants was not available for analysis. Stimulant medication users, like all participants, were instructed to take their medications as prescribed prior to exercise testing. However, the degree of compliance with this instruction is unknown and the timing of the last dose is unknown. Duration of stimulant use in this study is also unknown. Only current (i.e. prevalent) medications were ascertained, and former use of stimulants was unknown.

As strengths of this study, exercise parameters and baseline characteristics of participants were rigorously measured, and the propensity score matching technique yielded a sample of stimulant medication users and nonusers that was very similar on the observed participant characteristics. Over-the-counter drug supplement use was queried. The relatively large sample size is of great utility given the difficulty of conducting a large RCT that could compare chronic stimulant use versus chronic placebo.

5 Conclusions

In this propensity score-matched community sample undergoing a maximal exercise test, stimulant medication use was not associated with increases in peak SBP and average SBP rise, nor did it impact cardiorespiratory fitness (VO₂max). However, stimulant use was associated with a decreased peak HR as well as an increased risk of chronotropic incompetence. While chronotropic incompetence is an independent risk factor for cardiovascular morbidity and mortality, the clinical significance of stimulant-induced chronotropic incompetence is unknown. Further research is needed to further understand the implications of the findings of the current observational study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Stimulant medication use was associated with a significant decrease in peak heart rate.
2. Stimulant medication use was associated with an increased risk of chronotropic incompetence.
3. Stimulant medication use was not associated with changes in peak SBP, average SBP rise, or estimated VO_2max .

Figure 1.
Inclusion, exclusion, and propensity score matching of participants in the Cooper Center Longitudinal Study cohort.

Figure 2.

Histogram of the observed propensity score distribution in the cohort of propensity score-matched stimulant users and nonusers and pre-matched nonusers.

Table 1

Characteristics of Propensity Score-Matched Stimulant Medication Users and Nonusers and Pre-Matched Nonusers

Covariates	Matched Non-users (n=735)	Stimulant Medication Users (n=245)	Pre-Matched Non-users (n=19,499)
Age (years) ^a	42.3 (10.4)	42.2 (11.3)	48.1 (9.22)
Education (years) ^a	15.6 (2.48)	15.6 (2.51)	16.0 (2.45)
Sex (male), n (%)	387 (52.7%)	126 (51.4%)	13,224 (67.8%)
Race/ethnicity, n (%)			
Non-Hispanic white	703 (95.6%)	235 (95.9%)	18,268 (93.7%)
Other ^b	32 (4.4%)	10 (4.1%)	1231 (6.3%)
BMI ^a	27.0 (5.4)	26.7 (5.2)	26.5 (4.3)
Resting Systolic Blood Pressure (mmHg) ^a	118.4 (14.6)	117.5 (13.9)	120.3 (14.1)
Resting Diastolic Blood Pressure (mmHg) ^a	80.4 (10.7)	79.4 (11.1)	81.1 (9.81)
Resting Heart Rate (bpm) ^a	67.5 (11.7)	67.6 (11.7)	62.0 (10.2)
Year of Examination, 1995–2013 (data not shown)			
Self-Report of Alcohol use, n (%)	599 (81.5%)	197 (80.4%)	16,004 (82.1%)
Self-Report of Smoking, n (%)	148 (20.1%)	44 (18.0%)	2321 (11.9%)
Self-Report of Hypertension, n (%)	59 (8.0%)	17 (6.9%)	1292 (6.6%)
Self-Report of Family History Heart Disease, n (%)	142 (19.3%)	47 (19.2%)	5544 (28.4%)
Self-Report of Diabetes, n (%)	12 (1.6%)	4 (1.6%)	224 (1.2%)
Self-Report of High Cholesterol, n (%)	200 (27.2%)	67 (27.4%)	4845 (24.9%)
Self-Report of Lipid Lowering Medication, n (%)	68 (9.3%)	21 (8.6%)	1869 (9.6%)
Physical Activity Index, n (%)			
0	108 (14.7%)	35 (14.3%)	2167 (11.1%)
1	310 (42.2%)	98 (40.0%)	7266 (37.3%)
2	227 (30.9%)	73 (29.8%)	6573 (33.7%)
3	67 (9.1%)	32 (13.1%)	2533 (13.0%)
4	23 (3.1%)	7 (2.9%)	960 (4.9%)
Self-Report of Physical Activity (MET-minutes per week) ^a	1165.1 (1616.4)	1164.6 (2057.2)	1140.8 (1420.1)

^a Mean (Standard Deviation)

^b The small percentage of participants who did not self-identify as non-Hispanic white were combined into one category entitled “Other”

The Effect of Stimulant Medication Exposure on Peak SBP, Average SBP Rise, Peak Heart Rate, and VO₂max during the Maximal Treadmill Exercise Test in the Propensity Score-Matched Cohort while Adjusting for the 18 Covariates in the Model

Table 2

Log of Average SBP Rise									
Peak SBP					Log of Average SBP Rise				
Variable	Parameter Estimate	LS Mean Estimate	Standard Error	95% CI	p value	Parameter Estimate	LS Mean Estimate	Standard Error	p value
Stimulant Use	-0.91		1.48	(-3.82 to 2.00)	0.54 ^a	-0.023		0.030	0.44 ^b
Yes		179.7	3.56	(172.7 to 186.7)			1.48	0.073	(1.34 to 1.62)
No		180.6	3.39	(174.0 to 187.3)			1.50	0.069	(1.37 to 1.64)
VO ₂ max (mL/kg/min)									
Peak Heart Rate					VO ₂ max (mL/kg/min)				
Variable	Parameter Estimate	LS Mean Estimate	Standard Error	95% CI	p value	Parameter Estimate	LS Mean Estimate	Standard Error	p value
Stimulant Use	-4.24		0.86	(-5.93 to -2.55)	<.0001 ^c	0.65		0.37	0.083 ^d
Yes		170.2	2.02	(166.2 to 174.2)			34.8	0.88	(33.1 to 36.5)
No		174.4	1.92	(170.7 to 178.2)			34.2	0.84	(32.5 to 35.8)

^a FDR-adjusted p=0.54

^b FDR-adjusted p=0.54

^c FDR-adjusted p=0.0004

^d FDR-adjusted p=0.16

The Effect of Stimulant Medication Exposure on Peak SBP, Average SBP Rise, Peak Heart Rate, and VO₂max during the Maximal Treadmill Exercise Test in the Propensity Score-Matched Cohort Without Adjusting for the 18 Covariates in the Model

Table 3

Variable	Peak SBP					Log of Average SBP Rise				
	Parameter Estimate	LS Mean Estimate	Standard Error	95% CI	p value	Parameter Estimate	LS Mean Estimate	Standard Error	95% CI	p value
Stimulant Use	-2.36		2.00	(-6.29 to 1.58)	0.24 ^a	-0.040		0.035	(-0.11 to 0.029)	0.26 ^a
Yes		178.5	1.83	(174.9 to 182.1)			1.35	0.030	(1.29 to 1.41)	
No		180.8	1.16	(178.6 to 183.1)			1.39	0.018	(1.35 to 1.42)	
Variable	Peak Heart Rate					VO ₂ max (mL/kg/min)				
	Parameter Estimate	LS Mean Estimate	Standard Error	95% CI	p value	Parameter Estimate	LS Mean Estimate	Standard Error	95% CI	p value
Stimulant Use	-3.91		1.02	(-5.92 to -1.90)	0.0001 ^b	0.78		0.55	(-0.31 to 1.87)	0.16 ^a
Yes		175.5	0.93	(173.7 to 177.3)			37.0	0.49	(36.0 to 37.9)	
No		179.4	0.58	(178.3 to 180.5)			36.2	0.29	(35.6 to 36.7)	

^a FDR-adjusted p=.26.

^b FDR-adjusted p=.0004.