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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 VO_2max during exercise. A linear mixed model analysis was used to evaluate the effect of stimulant exposure on each of the exercise outcomes. In a 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_2max 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., 2015). 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.

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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_2max).

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 Fig. 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

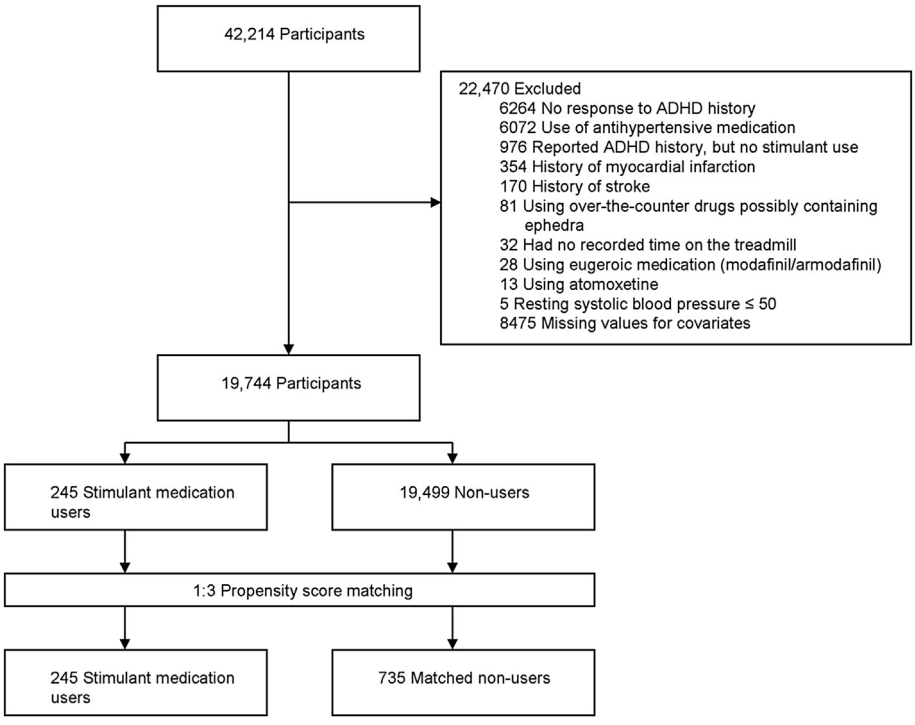

Fig. 1. Inclusion, exclusion, and propensity score matching of participants in the Cooper Center Longitudinal Study cohort.