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Objective aerobic fitness level and neuropsychological functioning in healthy adolescents and emerging adults: Unique sex effects

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ABSTRACT

Objective: Research suggests positive relationships between aerobic fitness and cognition in older adults; however, limited research has adequately investigated the relationship between objectively measured aerobic fitness and broad cognitive functioning in healthy adolescents and young adults without psychiatric or physical health disorders. Further, studies to date have disproportionately examined males and failed to examine sex differences. Here we examine the relationship between aerobic fitness and neuropsychological functioning in physically healthy youth and whether sex moderates these findings.
Design: Sixty-four healthy emerging adults (16-25 years-old; 32 female) underwent measurement of objective aerobic fitness (VO_2 max) and neuropsychological assessment. Exclusion criteria included: left-handedness, prenatal medical issues or alcohol/illicit drug exposure, Axis-I psychiatric disorders, major medical disorders including metabolic conditions such as diabetes, hypertension, hyperlipidemia, major neurologic disorders, LOS greater than 2 min, intellectual disability or learning disability, regular substance use (e.g., greater than bi-weekly use of cannabis) or positive drug toxicology testing.
Method: Multiple regressions examined VO_2 max, sex, sex*VO_2interaction in relation to neurocognition, controlling for objectively measured body fat percentage.
Results: Prior to including body fat percentage, higher VO_2 max related to improved working memory (Letter-Number Sequencing; $p = .03$) and selective attention (CPT-II hit response time standard error; $p = .03$). Aerobic fitness significantly interacted with sex, as higher-fit males had better performance on two sustained attention tasks while females did not demonstrate this pattern (CPT-II variability standard error, $p = .047$; Ruff 2&7 Total Speed, $p = .02$). Body fat percentage was positively slower cognitive flexibility (D-KEFS color-word switching/inhibition, $p = .046$).
Conclusions: VO_2 independently predicted better working memory and selective attention. Increased aerobic fitness level related to increased performance on sustained attention tasks in males but not females. Therefore, aerobic fitness may be positively related to better cognitive functioning in physically healthy adolescents and emerging adults without metabolic conditions. Further research into factors (e.g., intensity or type of activity) that may relate to beneficial outcomes by sex are needed.

1. Introduction

Physical fitness is an important marker of health, academic, and life outcomes (Fair, Reed, Hughey, Powers, & King, 2017; Hogstrom, Nordstrom, Eriksson, & Nordstrom, 2015; Taanila, Hemminki, Suni, Pihlajamaki, & Parkkari, 2011). Aerobic exercise, or exercise that stimulates the flow of oxygenated blood, is one means of improving aerobic fitness, and has been suggested to be particularly beneficial for neurocognitive outcomes (Hillman, Erickson, & Kramer, 2008). Findings are so promising that exercise, and therefore fitness, is often encouraged in childhood to promote neurodevelopment (Hillman & Biggan, 2017; Hillman et al., 2014) and targeted to reverse pathological conditions such as depression (Stanton & Reaburn, 2014), traumatic brain injury (Chin, Keyser, Dsurney, & Chan, 2015), dementia and

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cognitive decline (Behrman & Ebmeier, 2014; Langa & Levine, 2014). However, despite evidence of neural and cognitive maturation in adolescents and young adults (Gogtay et al., 2004) and the potential for greater sensitivity to intervention during this time period than earlier or later in the lifespan (Spear, 2013), the benefits of aerobic fitness in relation to neurocognition during adolescence and emerging adulthood have been limitedly studied; though the extant research is promising (for review, see (Herting & Chu, 2017). Further, studies that do exist often do not use objective measurement of aerobic fitness, are focused on acute effects of aerobic *exercise*, and/or utilize a limited cognitive battery, limiting knowledge applied to the full range of cognitive domains.

Multi-factorial mechanisms may be contributing to positive outcomes related to high levels of aerobic fitness due to aerobic exercise. Preclinical research suggests improved catecholaminergic function (Dunn et al., 1996; Elam, Svensson, & Thoren, 1987; Heyes, Garnett, & Coates, 1984; Waters et al., 2005) and decreased inflammatory response and oxidative stress ((Sakurai et al., 2009); for review, see (Radak, Kumagai, Taylor, Naito, & Goto, 2007)) related to aerobic exercise. In young animals (Kim, Lee, Kim, Yoo, & Kim, 2007; Liu, Diorio, Day, Francis, & Meaney, 2000) and in adolescents and young adults (Egan et al., 2003; Mueller et al., 2015; Whiteman et al., 2014) aerobic exercise appears to increase several brain growth factors. More specifically, aerobic exercise has been linked to increased release of brain-derived neurotrophic factor, insulin-like growth-factor-1, and vascular endothelial grow factor (Egan et al., 2003; Kim et al., 2007; Liu et al., 2000; Mueller et al., 2015; Whiteman et al., 2014), as well as higher level of circulating endocannabinoids (Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014). Research suggests many of these mechanisms (e.g., cell proliferation and neurogenesis, epigenetic expression) are particularly important during the adolescent and young adult period (for review, see (Gomes da Silva & Arida, 2015)). Each of these mechanisms may explain part of the beneficial relationships often demonstrated between aerobic fitness (as improved through exercise) and brain health.

Aerobic fitness is often measured through both self-report and objective measures of fitness (e.g., VO_2 maximum testing, a measurement of maximal oxygen consumption; (Myers et al., 2002), and aerobic exercise interventions are used to modify aerobic fitness level. Cross-sectional studies focusing on human youth have found links between aerobic fitness level and improved cognitive performance. For example, physical activity, measured by an accelerometer, was linked with superior attention (Vanhelst et al., 2016) in adolescents. Further, self-reported aerobic fitness relates to better executive functioning (Lee et al., 2014) and visuospatial learning (Herting & Nagel, 2012; Lee et al., 2014) in adolescents. However, self-report of aerobic fitness may not be reliable and not all physical activity may result in changes in aerobic fitness. The gold standard in measuring current aerobic fitness objectively is VO_2 maximum testing. Two studies have linked VO_2 maximum with brain structure reporting that aerobic fitness mediated the relationship between hippocampal viscoelasticity (a measure of tissue integrity) and better visuospatial memory in young adults (Schwarb et al., 2017), and that it was positively linked with right entorhinal volume and memory performance (Whiteman, Young, Budson, Stern, & Schon, 2016). Improved estimated and objective aerobic fitness in teens has also been linked with superior reaction time and selective attention (Pindus et al., 2015; Wengaard, Kristoffersen, Harris, & Gundersen, 2017) and visual working memory (Ross, Yau, & Convit, 2015). Together this suggests that aerobic fitness may be linked with superior executive functioning, learning, and memory even in physically healthy adolescents and young adults. However, in each of these studies, limited batteries were administered despite the wide range of cognitive functions that may be related to fitness. Further, few studies excluded participants with metabolic or obesity conditions.

A significant concern with the current literature is the disproportionately male samples and lack of investigations into sex differences (e.g., (Herting & Nagel, 2012; Wengaard et al., 2017). Despite known sex differences in patterns of neurodevelopment (Lenroot & Giedd, 2010), physical activity (Spencer, Rehman, & Kirk, 2015), and aerobic fitness level (VO_2 max) (Pescatello, 2014), sex has only occasionally been considered in most clinical studies of aerobic fitness and exercise in emerging adults. For example, in a within-subjects study of acute effects of aerobic exercise, resistance training, and no exercise, adolescent males benefitted more following an acute aerobic exercise paradigm on each version of a Stroop task compared to females (Harveson et al., 2016). In adults, however, aerobic exercise intensity significantly moderated IQ scores in women, but not in men (Killgore & Schwab, 2012). In a study of only women, individuals with better cardiovascular fitness demonstrated superior executive functioning than low-fit individuals, regardless of whether they were younger (19–34) or older adults (55–72) (Dupuy et al., 2015). While these studies assessed "healthy" individuals and excluded cardiovascular disease, they are limited in that they did not exclude metabolic disorders (e.g., hyperlipidemia, hypertension, diabetes) and did not measure adiposity or exclude obese participants; obesity is itself linked with poorer cognitive functioning in young adults (Huang, Chen, Shen, Fan, & Wang, 2019; Ross et al., 2015). Further, body fat and aerobic fitness level are related (Mondal & Mishra, 2017), and indeed are significantly correlated in the current sample, suggesting it is important to assess for the influence of adiposity on cognitive outcomes. Thus, more research is needed to examine the link between aerobic fitness, sex, and multiple domains of cognitive functioning in physically healthy adolescents and young adults without comorbid metabolic or obesity-related conditions.

The present study sought to investigate the relationship between aerobic fitness level, as objectively measured by maximal oxygen consumption, and broad neuropsychological functioning in healthy adolescent and young adults without comorbid metabolic or cerebrovascular conditions or controlling for body fat. Further, we aimed to assess whether sex moderates this relationship. We hypothesized that aerobic fitness would be significantly and positively associated with neuropsychological performance, particularly on tasks of executive functioning and attention. We then explored whether sex moderated these findings.

2. Materials and methods

2.1. Participants

Sixty-four healthy adolescents and emerging adults (38 low-fit, 26 high-fit) were recruited through local newspaper advertisements and fliers placed around the city for a larger parent imaging study which advertised as a healthy development study (R01 DA030354). The participants were recruited in order to be approximately balanced for active versus sedentary recent physical activity in order to sample a wide range of aerobic fitness levels. The age range (16–25 years old) was chosen given the unique circumstances that face emerging adults (defined as late adolescence, early adulthood, and often conceptualized as 16/17 to mid-20's) (Wood et al., 2018). Further, neuroanatomical (Lenroot et al., 2007) and cognitive changes (Yurgelun-Todd, 2007) abound during this time, particularly in regions and domains that support executive functioning (the highest order of cognitive functioning). Inclusion criteria included being a fluent English speaker between 16 and 25 years old, and fitting into the active or sedentary group. Exclusion criteria for all participants included: being left handed, MRI contraindications, past year co-morbid independent Axis-I disorders, major medical or neurologic disorders including metabolic-related disorders such as diabetes, hyperlipidemia and hypertension, smoking greater than two cannabis joints a week over the past year (>104 joints in past year), prenatal issues (e.g., gestation <35 weeks) or prenatal alcohol (>4 drinks/day or >7 drinks/week) or illicit drugs (>10 uses) exposure, or excessive drug use in lifetime (>50 uses of any drug category except nicotine, alcohol, or cannabis). Participants confirmed 21 days of abstinence from all alcohol and drug use (other than tobacco) through self-report and drug toxicology screen. The university IRB approved all aspects of this study.

Prior work from our group has similarly investigated fitness and cognition in an overlapping sample with the present study, though the focus of that analysis was on the influence of heavy substance use with inclusion criteria that required heavy use for many of the participants (Wade, Wallace, Swartz, & Lisdahl, 2018). That manuscript also did not investigate sex differences.

2.2. Procedure

2.2.1. Two-step screening process

To establish eligibility, participants first called in to a study line in response to flyers and advertisements around the community. Participants were verbally consented (or assented following consent from parent/guardian if under the age of 18). A 5–10 min phone screen was then completed. Both participants and one parent were separately screened to assess initial eligibility (e.g., age, ethnicity, MRI contraindications, medical history, and yes/no questions regarding psychiatric and, for the participant, substance use history). The second step included obtaining written consent/assent via mail; a 45-min detailed phone screen was then scheduled and completed. This screen consisted of a youth psychiatric history though the Mini International Psychiatric Interview (MINI) (Sheehan et al., 1998) completed separately by both the parent and participant, a questionnaire to ensure safety for VO_2 participation (Thomas S. et al., 1992), and the participant also reported on lifetime history of substance use via the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998; Stewart & Brown, 1995). Each participant and their respective parent were compensated $20 for their time for the detailed screening session.

2.2.2. Study sessions

Eligible participants completed five study sessions over the course of four weeks to monitor weekly physical activity and ensure abstinence from substances, with data from the fourth session presented here. Participants completed a full 3-h neuropsychological battery followed immediately by VO_2 maximum testing, and were compensated for their time.

2.3. Measures

2.3.1. Screening measures

Recent Physical Activity. During the initial phone screen, youth were asked how many times a week they engaged in moderate or vigorous physical activity for at least 10 min at a time. Answers were coded as "active" or "not active" based on whether they met 2007 criteria by the American College of Sports Medicine and American Heart Association (i.e, performing moderate-intensity aerobic physical activity for a minimum of 30 min on five days each week or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week) (Haskell et al., 2007). This group status was not utilized in the analyses, but rather to ensure adequate sampling of aerobic fitness levels.

Physical Activity Readiness Questionnaire. The PAR-Q (Thomas S. et al., 1992) was administered during the detailed screen to youth and parents to ensure all youth could complete the VO_2 maximum testing session.

Lifetime History of Substance Use. Lifetime frequency/quantity of lifetime usage, age of first use, age of regular use, and symptoms of substance use disorder for alcohol, nicotine and cannabis were measured through the Customary Drinking and Drug Use Record (CDDR), semi-structured interview (Brown et al., 1998; Stewart & Brown, 1995).

Mental Health Diagnoses. To ensure no past-year psychiatric comorbidities, participants (and parents of minors) were administered the semi-structured Mini International Psychiatric Interview (MINI) (Sheehan, Lecrubier, Sheehan, Amorim, Janavs, Weiller, Hergueta, et al., 1998) or the MINI-Kid (Sheehan et al., 2010).

2.3.2. Primary session measures

Past Year Substance Use. Standardized units of cannabis (joints), alcohol (standard drinks), and other drug use for the past year was calculated using a modified version of the Timeline Follow-Back (TLFB) (Lisdahl & Price, 2012; Sobell & Sobell, 1992). Urinalysis and breathalyzer tests confirmed abstinence and assessed for recent nicotine exposure.

Physical Activity Levels. Physical activity levels for the week prior to neurocognitive and VO_2 maximum testing were measured with Triaxial accelerometer data (measured by the ActiGraph wGT3X-BT). Triaxial accelerometers are a valid estimate of activity in youth (Hale, Pal, & Becker, 2008; Rowlands & Eston, 2005) and adults (Hale et al., 2008). The wGT3X-BT is a battery powered, triaxial research grade activity monitor that measures movement across three orthogonal planes: vertical (x), anteroposterior (y), and mediolateral (z). Here we analyzed the most recent week's average daily moderate-to-vigorous physical activity (with cut-offs consistent with (Freedson, Melanson, & Sirard, 1998) and average daily sedentary behavior (with cut-offs consistent with (Matthews et al., 2008) as estimates of overall activity (Kang et al., 2009). In this sample, moderate-to-vigorous physical activity significantly correlated with VO_2 maximum performance ($r = 0.39$, $p = .003$).

Body Fat Composition. Body height and mass were measured using standard procedures (Pescatello, 2014). In addition, a Tanita SC-331S Body Composition Monitor (Tanita, Arlington Heights, IL) was used to measure additional adiposity characteristics, such as weight, BMI, and total body fat percentage.

Aerobic Fitness (VO_2 maximum). Participants were asked to refrain from food and caffeine for 4 h prior to the exercise tests. Body height and mass were measured using standard procedures (Pescatello, 2014). Prior to each exercise test, the metabolic measurement system, ParvoMedics TrueOne 2400 (ParvoMedics, Salt Lake City, UT) was calibrated according to the manufacturer's instructions using a 3 L syringe for the pneumotachometer, and a two-point calibration for the gas analyzers (room air and a certified gas 4.08% CO_2, 115.98% O_2, balance N_2). Participants were fitted with the rubber mouthpiece connected to a Hans Rudolf 2700 series two-way nonrebreathing valve (Kansas City, MO), noseclip, and heart rate strap (Polar Wearlink 31, Finland) for the collection of expired gases and measurement of heart rate. Participants completed a maximal incremental exercise test on a treadmill (Full Vision Inc., TMX425C Trackmaster, Newton, KS) following the Bruce Protocol until volitional fatigue. Expired gases were measured continuously using a ParvoMedics TrueOne 2400 metabolic measurement system (ParvoMedics, Salt Lake City, UT); this has been shown to be a valid measure of expired gases at rest and during increasing intensities of activity (Bassett et al., 2001). Criteria for determination of attainment of VO_2 max were based on those recommended by Howley and colleagues and normed by age and sex (Howley, Bassett, & Welch, 1995). Metabolic data were averaged over 1 min and exported into a spreadsheet for analysis.

Neuropsychological Battery. Neuropsychological domains were assessed with the following cognitive tasks:

Estimated IQ. The *Wide Range Achievement Test-4*th *edition* (WRAT-4) (Manly, Jacobs, & Touradji, 2002) Word Reading subtest was used to measure estimated IQ. Participants were instructed to read aloud from a list of words. The normed total score was used.

Executive Functioning. Executive functioning and decision making was measured using the *Wisconsin Card Sort Task – 64 Cards* (WCST-64) (Kongs, Thompson, Iverson, & Heaton, 2000). For the WCST-64, participants had to correctly integrate examiner feedback of correct/incorrect responses regarding how to categorize a stake of cards with no further direction; Total Categories Completed (raw) were used. In addition, *Delis-Kaplan Executive Functioning Scale* (D-KEFS) (Delis, Kaplan, & Kramer, 2001) Color-Word Interference-Switching Condition (variable: scaled score) was used to measure cognitive inhibition. In the Color-Word Interference-Switching task, participants had to name the color of the word they were reading while inhibiting reading the word;

participants had to do the reverse (read the word, not name the color) when the item was in a box.

Sustained Attention. In the *Ruff 2&7* (Ruff & Allen, 1996), participants have to go line by line and mark every 2 and 7 that they see within a short timespan (variables: total accuracy and total speed normed scores). In *Conner's Continuous Performance Task, 2*nd *Edition* (CPT-II) (Conners, 2000), participants must respond to every stimulus letter except a specified letter which indicates the participant should not response (i.e., inhibition their response). Normed scores for variability standard error (a measure of within-subject consistency) and hit response time standard error (overall consistency) were used to assess sustained attention.

Verbal Memory. Verbal memory was measured through the *California Verbal Learning Test-II* (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000), wherein participants hear a list of words and repeat back as many of those words as they can remember several times, after hearing and reciting a second list with different words, they must again recite the first list from memory. After a delay, participants are asked to repeat the first list of words again. Finally, participants are read a list of words and must say whether or not the word was from the first list. Immediate memory was measured by immediate recall total normed score (T1-5) and delayed recall was measured by long-delay free recall normed score.

Working Memory. In the *Wechsler Adult Intelligence Scale, Third Edition* (WAIS-III) (Wechsler, 1997) Letter-Number Sequencing (LNS), participants listen to a list of letters and numbers, then must recite them back in alphabetical then numerical order. Working memory was measured through LNS total scaled score.

Measurement of Effort. An embedded effort measure from the CVLT-II (Forced Choice) was assessed to ensure proper engagement by participants; all participants demonstrated adequate engagement, performing above cut-offs for embedded effort.

2.4. Power analysis

G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009) was used to confirm needed sample size to detect moderate to large effects. Results indicate that a sample size of 62 is sufficient to detect effect sizes (f^2) of 0.3 (with power = .95 at $\alpha = 0.05$).

2.5. Data analysis

Data analysis was completed using SPSS 26.0, and all statistical decisions were made at $p < .05$. High- and low-fit groups were created based on the 50th percentile split of VO_2 maximum performance by age and sex (see above) (Pescatello, 2014); this group status was only used for the selection of covariates and to aid in describing the study sample. The continuous variable of VO_2 maximum performance was used in the regressions. Between-group differences on demographic variables were measured with analyses of variance (ANOVAs) and $\chi 2$ tests; two sets of analyses were run: one with high v. low fit groups, and one with male v. female groups. Given the wide age range included in this study, age was considered as a potential covariate. However, as all cognitive and aerobic fitness performance was age-normed or scaled, it was decided that age should not be included as a covariate as this would overcorrect for age. Controlling for fat percentage, multiple regressions were run, assessing VO_2 max, sex, and body fat percentages, and sex*VO_2 interaction.

3. Results

3.1. Demographics

Overall, participants were 50% female, 70% Caucasian, and 91% non-Hispanic. Aerobic fitness groups did not differ significantly by ethnicity, race, sex, estimated IQ, education, past-year cannabis use, past-year alcohol use, recent nicotine exposure (cotinine level), or amount of sedentary behavior (see Table 1). As expected, the groups did differ by sex- and age-normed VO_2 max performance ($F(1,62) = 83.22$, $p < .001$), total body fat percentage ($F(1,61) = 9.32$, $p = .003$), BMI ($F(1,62) = 4.92$, $p = .03$), and approached significant difference in average daily moderate-to-vigorous physical activity ($F(1,55) = 3.83$, $p = .06$). When assessing for differences by sex, males and females differed by sex- and age-normed VO_2 max ($F(1,62) = 24.41$, $p < .001$; males demonstrated higher VO_2 max), and total body fat percentage ($F(1,61) = 44.25$, $p < .001$; females demonstrated higher body fat percentage). Males also had higher average daily moderate-to-physical activity than females ($F(1,55) = 7.29$, $p = .009$). Although body fat percentage and BMI were both significantly different, given their strong correlation, only fat percentage was included as a covariate in all analyses. Distributions of VO_2 performance and body fat by sex are presented in Figs. 1 and 2.

3.2. Primary findings

All regressions from the final model (including all variables and covariates) are presented in Table 2.

3.3. VO_2 max

Higher VO_2 max performance was independently associated with superior working memory and selective attention as measured by LNS (beta = 0.27, $t = 2.19$, $p = .03$, $f^2 = 0.08$) and reduced CPT-II hit response time consistency (beta = −0.27, $t = -2.17$, $p = .03$, $f^2 = 0.08$); however, these relationships were no longer significant once the sex*VO_2 interaction and body fat percentage were included.

*3.4. VO_2 max*Sex*

Sex moderated the relationship between VO_2 max and performance on measures of sustained attention: CPT-II variability standard error (beta = 0.25, $t = 2.03$, $p = .047$, $f^2 = 0.04$; Fig. 3) and Ruff 2&7 total speed (beta = −0.31, $t = -2.41$, $p = .02$, $f^2 = 0.10$; see Fig. 4). Investigation of the scatterplot revealed that males had more robust relationship between higher aerobic fitness and superior sustained attention, while females demonstrated a negative relationship between sustained attention and aerobic fitness.

3.5. Covariates

Increased total body fat percentage was significantly related to longer time to complete D-KEFS color-word switching/inhibition (beta = −.41, $t = -2.04$, $p = .046$, $f^2 = 0.07$). Sex was not independently related to performance on any cognitive tasks.

4. Discussion

Here we investigated whether aerobic fitness (measured objectively by VO_2 max performance) was associated with neuropsychological functioning in healthy adolescents and emerging adults without significant psychiatric, substance use, or physical health conditions. By itself, increased aerobic fitness was associated with improved working memory and detectability on a selective attention task. Primary results suggested that sex interacted with aerobic fitness in predicting sustained and selective attention even after controlling for total body fat percentage, in that males demonstrated a positive relationship between aerobic fitness and performance while females did not demonstrate this pattern.

Consistent with most common neurocognitive findings associated with aerobic fitness in adolescents and emerging adults (Ciria, Perakakis, Luque-Casado, Morato, & Sanabria, 2017; Pindus et al., 2015; Wengaard et al., 2017), our results suggest that current aerobic fitness levels are associated with tasks of selective attention in physically

Table 1
Demographics, substance use, and fitness characteristics by fitness group and gender.

	Low-Fit Males (n = 16) % or *M* (SD) Range	Low-Fit Females (n = 22) % or *M* (SD) Range	High-Fit Males (n = 16) % or *M* (SD) Range	High-Fit Females (n = 10) % or *M* (SD) Range
Age (years)	21.44 (2.63) 16–25	21.23 (2.56) 16–25	20.13 (2.39) 16–25	22.20 (2.35) 18–25
Education	14.75 (2.59) 9–19	14.50 (2.13) 11–21	13.75 (2.05) 10–16	14.90 (1.97) 12–17
Reading Score (WRAT-IV)	107.31 (10.64) 92–133	104.86 (10.47) 87–133	108.25 (11.79) 90–129	102.50 (9.20) 90–120
% Caucasian	75%	55%	81%	80%
% Not Hispanic/Latino/a	94%	82%	100%	90%
Past Year Cannabis Use (joints)	12.55 (23.78) 0–81.17	7.44 (22.06) 0–92.10	11.11 (23.41) 0–80.49	19.37 (30.96) 0–90.50
Past Year Alcohol Use (standard drinks)	223.66 (253.86) 0–756.50	95.7 (170.64) 0–800	187.98 (85) 0–694	193.35 (272.31) 0–883
Cotinine level	1.69 (1.25) 0–4	1.27 (1.03) 0–5	1.33 (1.18) 0–5	1 (.47) 0–2
*VO_2 Peak Performance (mL/kg/min)	40.02 (5.56) 28.60–45.40	31.95 (4.83) 20.80–39.20	53.15 (5.15) 46.90–62.90	45.77 (5.65) 41.10–60.10
*BMI (kg/m2)	25.15 (6.50) 17.4–40.4	25.58 (5.67) 18.7–39.1	22.09 (2.38) 18–26.1	23.43 (1.99) 19.9–27.2
*Body Fat (%)	19.03 (9.72) 6.4–41.7	29.99 (8.62) 16.8–47.2	12.09 (3.44) 6.7–18.3	26.38 (4.39) 16.3–31.8
Moderate- to Vigorous-Intensity Physical Activity (Minutes/Day)	43.24 (25.53) 14–110.33	27.29 (15.13) 6.50–65.71	47.71 (19.44) 13.86–89.00	39.97 (19.22) 15–68.33
Sedentary Behavior (Minutes/Day)	695.08 (175.31) 413.00–982.14	666.31 (209.41) 315.00–1030.43	623.95 (154.90) 364.00–878.80	675.67 (170.96) 447.00–947.00

Note. M = mean; SD = standard deviation. *$p < .05$

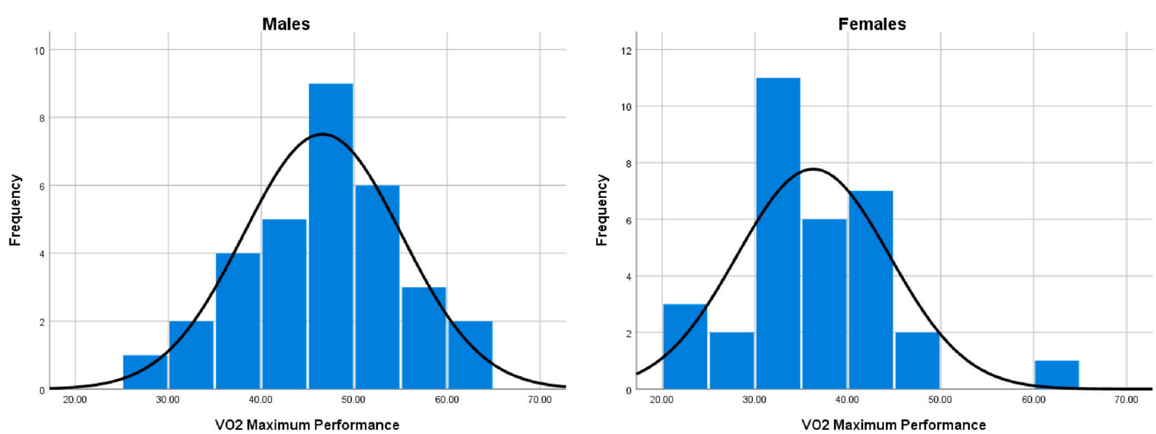

Fig. 1. Histogram of VO_2 maximum performance by sex, with males on the left and females on the right

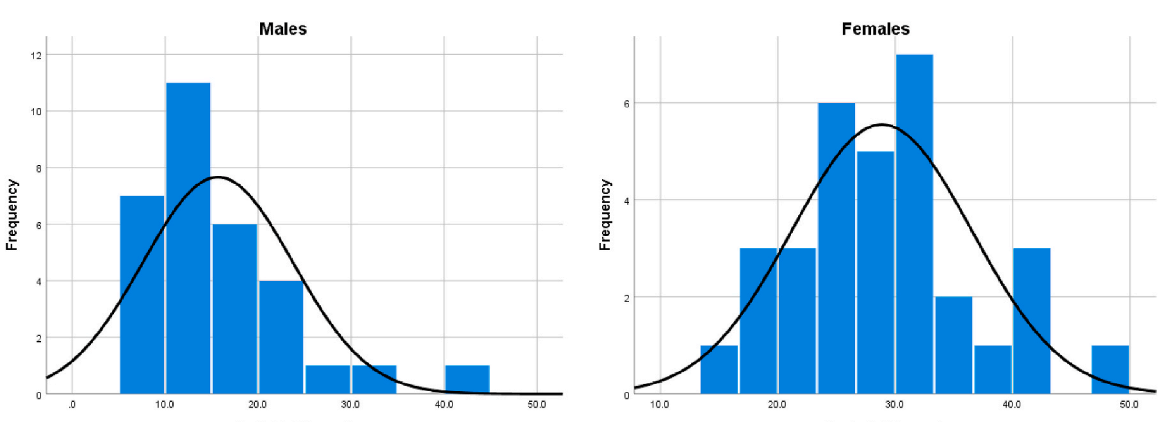

Fig. 2. Histogram of body fat percentage by sex, with males on the left and females on the right

Table 2
Primary regression results.

Cognitive Task	Variables	Beta	P-value	R^2
WCST-64 Total Categories	VO_2 max	-.071	.695	.030
	Sex	.059	.732	
	Body fat %	.006	.978	
	Sex*VO_2	.128	.338	
D-KEFS Color-World Interference-Switching	VO_2 max	-.148	.402	.071
	Sex	.152	.371	
	Body fat %	-.407	**.046**	
	Sex*VO_2	.100	.443	
Ruff 2&7 Total Accuracy	VO_2 max	.286	.113	.052
	Sex	.027	.877	
	Body fat %	.264	.197	
	Sex*VO_2	.032	.807	
Ruff 2&7 Total Speed	VO_2 max	.009	.960	.093
	Sex	-.011	.950	
	Body fat %	.017	.930	
	Sex*VO_2	−0.307	**.019**	
CPT-II Variability Standard Error	VO_2 max	-.159	.352	.132
	Sex	-.104	.528	
	Body fat %	.151	.438	
	Sex*VO_2	.253	**.047**	
CPT-II Hit Response Time Standard Error	VO_2 max	-.205	.229	.143
	Sex	-.154	.347	
	Body fat %	.199	.305	
	Sex*VO_2	.202	.108	
CVLT-II Immediate Recall	VO_2 max	.049	.785	.043
	Sex	-.149	.390	
	Body fat %	.024	.907	
	Sex*VO_2	.123	.350	
CVLT-II Delayed Recall	VO_2 max	.065	.714	.051
	Sex	-.225	.193	
	Body fat %	.176	.388	
	Sex*VO_2	.108	.410	
WAIS-III Letter Number Sequencing	VO_2 max	.215	.208	.144
	Sex	-.319	.054	
	Body fat %	.170	.379	
	Sex*VO_2	-.146	.245	

Note.p-values <.05 are indicated in bold. Only the final model with all variables and covariates are presented in this table.

healthy adolescents and young adults. Similarly, in a large study of adolescents that excluded for ADHD diagnosis, better processing speed in a stop-signal task was related to higher aerobic fitness (Pindus et al., 2015). In contrast with our hypotheses, we did not find a relationship between executive functioning and aerobic fitness level. Prior research has indicated executive functioning is better in high-fit older adults, but there was no relationship in high-fit younger adults (Hayes, Forman, & Verfaellie, 2016), perhaps suggesting a change in impact by age and a potential impact of higher rates of comorbid metabolic and vascular conditions in older adults. Notably, numerous other studies have similarly reported null results (see (Diamond & Ling, 2016). We also found body fat was negatively associated with executive functioning (inhibitory control), though most other studies have not controlled for this factor. Aerobic fitness, therefore, may represent a unique means of improving aspects of attention and should be investigated longitudinally in the future to better infer causality while also adequately accounting for potential moderators, like sex and age. In addition, aerobic exercise interventions could also be used to assess the utility of exercise, regardless of fitness level, for improving attention in emerging adults.

A number of mechanisms likely contribute to the present findings. Brain growth factors such as brain-derived neurotropic factor, insulin-like growth-factor-1, and vascular endothelial growth factor all are released following aerobic exercise (Egan et al., 2003; Kim et al., 2007; Liu et al., 2000; Mueller et al., 2015; Whiteman et al., 2014). Having increased levels of such growth factors leads to increased cell proliferation, neurogenesis, and dendritic branching (see (Cotman, Berchtold, & Christie, 2007; Llorens-Martin, Torres-Aleman, & Trejo, 2008). Further, inflammation is decreased in response to exercise (Radak et al., 2007; Sakurai et al., 2009) and inflammation can reduce growth factor activity (Cotman et al., 2007). Thus, reduced inflammation interacts with growth factors to improve cognitive performance. Exercise also influences catecholaminergic, or epinephrine and norepinephrine, function (Chaouloff, 1989; Dunn & Dishman, 1991; Dunn et al., 1996; Elam et al., 1987; Heyes et al., 1984; Waters et al., 2005), which in turn interact with other neurotransmitter and growth factor systems to stimulate cognition (McMorris, 2016).

Interestingly, though aerobic fitness was not related to executive functioning, a significant relationship was revealed between body fat and cognitive flexibility. BMI has been linked with executive

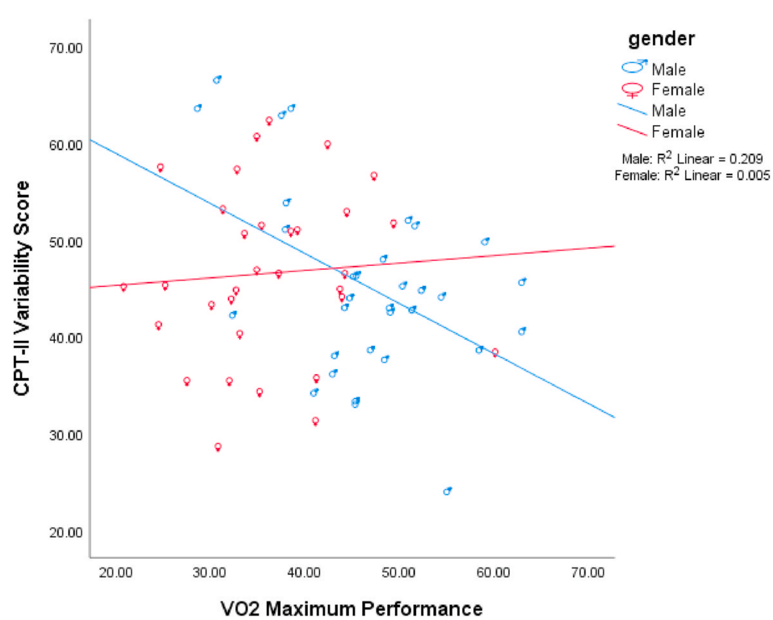

Fig. 3. Scatterplot of VO_2 maximum performance and CPT-II Variability by gender.
Note. Higher aerobic fitness level (higher VO2 maximum performance) related to better (lower normed performance) variability as measured by the CPT-II in males. For males, y = 69.26–0.52*x; for females, y = 43.79 + 0.08*x.

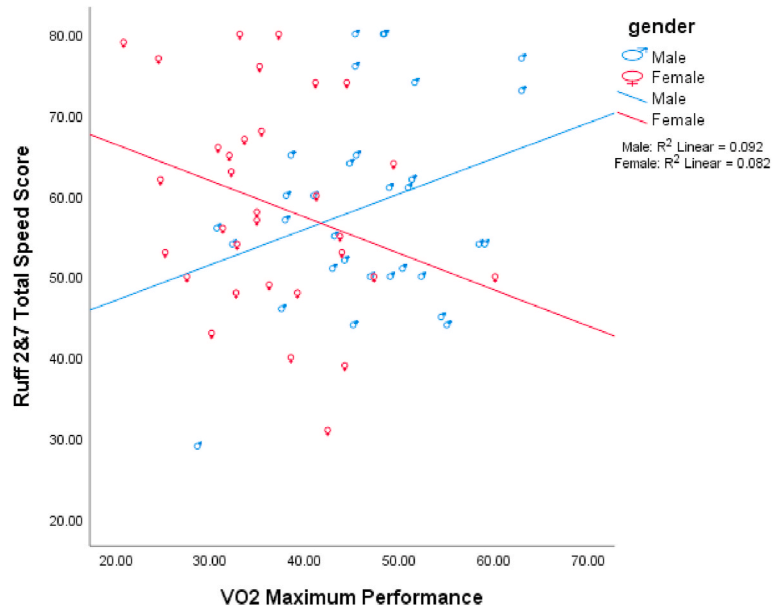

Fig. 4. Scatterplot of VO_2 maximum performance and Ruff 2&7 Total Speed score by gender.
Note. Higher aerobic fitness level (higher VO2 maximum performance) related to quicker (higher summed normed performance) total speed on the Ruff 2&7in males, with lower fitness level relating to quicker total speed in females. For males, y = 38.29 + 0.44*x; for females, y = 75.34–0.45*x.

functioning, especially impulsivity, response inhibition and negative urgency, in adolescents and young adults (Chamberlain, Derbyshire, Leppink, & Grant, 2015; Cole, Yen, Dudley-Javoroski, & Shields, 2019; Delgado-Rico, Rio-Valle, Gonzalez-Jimenez, Campoy, & Verdejo-Garcia, 2012; Huang et al., 2019; Lokken, Boeka, Austin, Gunstad, & Harmon, 2009). These findings are consistent with neuroimaging evidence reporting that obese adolescents display global decreases in white and gray matter, including in key regions for executive functioning including the orbitofrontal cortex (Maayan, Hoogendoorn, Sweat, & Convit, 2011; Yokum, Ng, & Stice, 2012). This may be because increased adiposity may influence cognition through increased circulating inflammatory cytokines, such as interleukin-6, interleukin-1β, fibrinogen, and C-reactive protein (Doupis et al., 2011), and due to abnormal levels of BDNF (Gray et al., 2005; Kernie, Liebl, & Parada, 2000; Rios et al., 2001). It is also possible that executive functioning deficits are not a result of increased adiposity, but are premorbid conditions that lead to binge eating and food addiction (Michaelides, Thanos, Volkow, & Wang, 2012; VanderBroek-Stice, Stojek, Beach, vanDellen, & MacKillop, 2017). Prospective longitudinal studies, such as the Adolescent Brain Cognitive Development (ABCD) Study, are needed to examine these relationships over time.

The main cognitive findings suggest that increased aerobic fitness may be beneficial for cognition, especially in males. This may be due to structural changes in neuronal areas underlying working memory and complex attention. For example, aerobic fitness in children has been linked to larger subcortical structures (Chaddock et al., 2010), improved white matter integrity in the corticospinal tracts and forceps minor in male adolescents (Herting, Colby, Sowell, & Nagel, 2014), larger hippocampal volumes (Herting & Nagel, 2012), increased right rostral middle frontal volume (Herting, Keenan, & Nagel, 2016), and reduced cortical thickness in young adults (Williams et al., 2017). Larger basal ganglia volumes have also been linked to better attention control performance in high-fit children regardless of sex (Chaddock et al., 2010). In addition, the actual neuroanatomical microstructure may be influenced through mechanisms such as influencing brain growth factors (Egan et al., 2003; Kim, Wittenberg, & Nam, 2017; Liu et al., 2000), catecholamines (Dunn & Dishman, 1991; Dunn et al., 1996), inflammation (Radak et al., 2007), and release of endocannabinoids that impact oligodendritic activity (Gomez et al., 2010; Molina-Holgado et al., 2002).

Despite limited evidence for the independent influence of sex on cognitive outcomes (Hyde, 2016), the present results suggest that sex may be an important moderator in the influence of aerobic fitness predicting selective and sustained attention performance. Indeed, our results observed in the higher-fit males are consistent with male-only findings (Wengaard et al., 2017). While the exact reason cognitive performance may vary by sex and fitness is unclear, a few reasons may be considered. First, sex may moderate the effectiveness of aerobic exercise on increasing levels of BDNF, as factors such as menstrual cycles and epigenetic polymorphisms influence BDNF expression (see (Barha & Liu-Ambrose, 2018). Respiratory and cardiovascular system anatomical differences may further contribute (Barha & Liu-Ambrose, 2018). Cultural differences are also noted to likely influence differential findings of sex on stereotypical cognitive performance, as certain countries do not consistently demonstrated "expected" patterns of male or female performance (Miller & Halpern, 2014). Likely a mix of biological and psychosocial explanations contributed to the sex and fitness interactions found in the present sample.

It may be important to highlight, too, that women may have their own unique strengths in relation to cognitive functioning and aerobic fitness. Dupuy and colleagues (Dupuy et al., 2015) found improved executive functioning in women as measured by a computerized version of the Stroop task, a different version of the Stroop task than given in the present study; their version may have a greater range in performance and may be more sensitive in detecting smaller effect sizes. As females in this study demonstrated lower VO_2 maximum level and less moderate-to-vigorous activity in the past week, perhaps they are not reaching a high enough level of aerobic fitness to impact downstream cognitive improvements. Alternatively, females may be engaging in other behaviors that counteract the positive impact of aerobic fitness. For example, though there was no significant difference in substance use by sex, females reported higher levels of substance use. As prior research suggests females may be more vulnerable to the neurocognitive impact of substances (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crane, Schuster, Mermelstein, & Gonzalez, 2015; Squeglia, Schweinsburg, Pulido, & Tapert, 2011), the present sample's substance use may be impacting aspects of cognitive functioning, though past-year use was low and was used as an exclusion factor. In addition, subtle differences in neurodevelopment and cognition due to stages of puberty and sex hormones have been found previously (Schulz & Sisk, 2016; Sullivan et al., 2016), but were not accounted for here. Perhaps aerobic fitness in females during mid-adolescence would have a detectable impact, given they tend to undergo neurodevelopment earlier. Taken together, the scant research suggests a need for greater consideration of sex across all research, including in neuropsychological functioning and physical fitness.

Admittedly, the cognitive performance differences exhibited are small; however, if exercise and fitness can improve cognition, it is worthwhile to consider how it may have a positive ripple effect into other life areas. For example, higher levels of cognition have been linked to higher income (Mollerstrom & Seim, 2014), higher life satisfaction (Jones, Rapport, Hanks, Lichtenberg, & Telmet, 2003), better leadership abilities (Judge, Colbert, & Ilies, 2004), socioeconomic status (von Stumm & Plomin, 2015), and lower risk of death (Whalley & Deary, 2001). Therefore, even small changes may allow for an optimization of neural development during adolescence and emerging adulthood and translate to much more significant life outcomes. Relatedly, as this was a physically healthy sample without significant comorbid substance use or Axis I psychiatric disorders; the full impact of aerobic fitness may be greater in youth with metabolic disorders, substance use, or psychiatric disorders that negatively impact neurocognition.

Prior research by our group suggests that substance use and aerobic fitness interact in predicting cognitive functioning (Wade, Wallace, Swartz, & Lisdahl, 2018). Others have also found aerobic fitness may influence clinical outcomes in substances users (Buchowski et al., 2011; Henchoz et al., 2014). Aerobic fitness and substance use may interact due to influencing common neurochemical pathways. For instance, regular cannabis use downregulates or decreases activation in cannabinoid 1 receptors (Hirvonen et al., 2012), while aerobic exercise upregulates or increases activity in this same receptor (Ferreira-Vieira, Bastos, Pereira, Moreira, & Massensini, 2014). Circulating endogenous cannabinoids (which components of cannabis mimic and bind to) are also associated with cognitive functioning (Lee & Gorzalka, 2012) and increased in response to aerobic exercise (Koltyn et al., 2014). For this reason, we excluded participants with heavy substance use from the present study.

Together, these results suggest an important relationship between aerobic fitness level, sex, and cognitive functioning in adolescents and emerging adults. However, limitations should be noted. These results are cross-sectional in nature and so causal directionality cannot be established. Additional longitudinal studies tracking the impact of aerobic fitness on neurocognition from childhood into adolescence and young adulthood are needed to determine causality. While we have extended the science into sex as an important moderator of aerobic fitness and cognition, many other potential moderators exist. For example, genetic variations, such as in BDNF, may be an important predictor of improved cognitive functioning in relation to aerobic fitness (Herting et al., 2016). This sample of adolescents and emerging adults were carefully screened to ensure health status, including lack of psychiatric comorbidity, metabolic disorders, and/or heavy substance use; the present results are therefore limited to healthy youth. Finally, balancing concern for Type I and Type II error is a challenge. Given the relatively small sample size, power was limited, thus inflating the likelihood of Type II error. To minimize this possibility, correction for multiple comparisons was not employed, necessitating replication in the future.

In summary, greater aerobic fitness (measured by objective measurement of VO_2 maximum) was associated with superior working memory and discrimination ability during a selective attention task in adolescents and young adults. Further, aerobic fitness interacted with sex, as higher fit males demonstrated better sustained attention accuracy and speed compared to low fit males. These findings highlight the potential cognitive benefits of aerobic fitness level on emerging adults, especially in males. Continued emphasis on aerobic fitness in youth appears important for both cognitive and other life outcomes. Large, longitudinal studies, such as the ABCD study (abcdstudy.org) can help elucidate causal relationships between aerobic fitness and neurodevelopment and clarify potential moderating factors such as sex, adiposity, and genetics.

CRediT authorship contribution statement

Natasha E. Wade: Conceptualization, Formal analysis, Data curation, Writing - original draft. **Christine M. Kaiver:** Data curation, Writing - review & editing. **Alexander L. Wallace:** Data curation. **Kelah F. Hatcher:** Data curation. **Ann M. Swartz:** Methodology, Writing - review & editing. **Krista M. Lisdahl:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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