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Aerobic exercise increases cortisol awakening response in older adults

Lauren L. Drogos[a,b], Katherine Wynne-Edwards[c], Ruokun Zhou[c], Samantha E. Hall[a,b], Amanda V. Tyndall[a,b], R. Stewart Longman[b,d,e,f], Gail Eskes[h], Marc J. Poulin[a,b,d,g,i,*]

[a] University of Calgary, Department of Physiology & Pharmacology, Canada
[b] University of Calgary Hotchkiss Brain Institute, Canada
[c] University of Calgary, Faculty of Veterinary Medicine, Canada
[d] University of Calgary, Department of Clinical Neurosciences, Canada
[e] University of Calgary, Department of Psychology, Canada
[f] Alberta Health Services, Foothills Medical Centre, Canada
[g] University of Calgary Libin Cardiovascular Institute of Alberta, Canada
[h] Dalhousie University, Departments of Psychiatry, Psychology & Neuroscience, Canada
[i] University of Calgary, Department of Faculty of Kinesiology, Canada

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ABSTRACT

Evidence from both preclinical and clinical studies suggests aerobic exercise may dampen age-related decline in cognitive performance. Alterations in hypothalamic-pituitary-adrenal (HPA) axis function and reactivity may be a mechanism by which aerobic exercise benefits cognitive performance, and reduces perceived stress. This investigation was completed as an ancillary investigation of the *Brain in Motion* (BIM) study, a 6-month supervised aerobic exercise intervention. Participants were generally healthy and screened for inclusion/exclusion criteria for the parent study. Thirty-eight participants were recruited (Mean age = 65.0 [SD = 5.1]; 60% female) and the final longitudinal sample was 32 participants. Participants provided a passive drool sample at: waking, 15, 30, and 45 min post-waking to assess the cortisol awakening response (CAR) and 3, 6, 9, and 12 h post-waking to assess daily area under the curve for cortisol. Salivary cortisol was quantified by liquid chromatography coupled to tandem mass spectrometry. The exercise intervention increased CAR but no differences were observed in daily AUC. In addition, larger increases in CAR were positively associated with greater decreases in subjective stress. Thus, aerobic exercise improved the CAR in otherwise healthy, but sedentary older adults and greater improvements in CAR were associated with greater reductions in perceived stress.

1. Introduction

Cortisol is a glucocorticoid hormone released by the adrenal glands in response to both psychological and physiological stress. Basal, or baseline, levels of cortisol rise with age in both men and women (Halbreich et al., 1984; Sherman et al., 1985); suggesting that as we age, the hypothalamic-pituitary-adrenal (HPA) axis can become disrupted. In healthy adults, after waking in the morning, cortisol levels quickly increase and then taper across the morning hours (Stalder et al., 2016; Wust et al., 2000a). This portion of the diurnal pattern is known as the cortisol awakening response (CAR). Total daytime area under the curve (AUC_d) is a reasonable estimate of unstimulated HPA activity, however, morning AUC as a marker of CAR has been shown to be a more sensitive marker of small changes to the HPA (Stalder et al., 2016; Wust et al., 2000a). CAR has higher intra-individual stability compared to single time point cortisol collection (Clow et al., 2004; Hellhammer et al., 2007). In addition, there is evidence that it is a distinct phenomenon from the circadian rhythm of cortisol (Clow et al., 2010a, b; Clow et al., 2004). There are many factors which can impact a single cortisol sample, the strongest being time of day. In the absence of an acute stressor, peak values of cortisol are expected within the first hour after awakening, and the lowest levels reached towards midnight (Clow et al., 2010a, b; Clow et al., 2004).

The CAR also changes with increasing age, specifically, there is a flattening of the diurnal pattern (Deuschle et al., 1997; Kudielka et al., 2003). In healthy adults, the CAR has been described as an increase in cortisol levels by approximately 50% within the 30 min after awakening (Pruessner et al., 1997; Schmidt-Reinwald et al., 1999; Stalder et al., 2016; Wust et al., 2000a, b). Abnormal patterns in CAR (i.e., blunted or attenuated awakening response) have been linked to

* Corresponding author at: Department of Physiology & Pharmacology Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Heritage Medical Research Building, Room 210, 3330 Hospital Drive NW, Calgary, Alberta, T2N 4N1, Canada.
E-mail address: poulin@ucalgary.ca (M.J. Poulin).

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systemic illnesses like chronic fatigue (Roberts et al., 2004), Type II diabetes (Bruehl et al., 2009), cardiovascular disease (Wirtz et al., 2007), and autoimmune diseases (Clow et al., 2004). Abnormal patterns in CAR have also been linked to psychiatric diseases like PTSD, depression and chronic stress (Bhagwagar et al., 2005; Huber et al., 2006, Wust et al., 2000a), as well as mild cognitive impairment (Lind et al., 2007), and dementia (Wahbeh et al., 2008). Beyond the direct role of cortisol in the etiology of cognitive decline, cardiovascular disease, type II diabetes, and depression are all significant risk factors for cognitive decline (Barnes and Yaffe, 2011).

There is also increasing evidence that cortisol may be a marker of disruption in the hippocampus, a brain area necessary for memory formation. The hippocampus is also involved in the negative feedback control of the HPA axis (Jacobson and Sapolsky, 1991; Zschucke et al., 2015). In animal models, glucocorticoids have been associated with detrimental effects on learning and memory retrieval, deleterious changes in cellular morphology within the hippocampus, decreases in long term potentiation, and the severity of hippocampal atrophy (Foy et al., 1987; Lupien and McEwen, 1997; McEwen et al., 2015; Roozendaal, 2002; Starkman et al., 1992, 2001; Starkman et al., 1999; Woolley et al., 1990). In Alzheimer's disease, serum and cerebrospinal fluid cortisol levels have been positively associated with hippocampal lesion size and disease progression (Csernansky et al., 2006; Davis et al., 1986; de Leon et al., 1988; Miller et al., 1998; Nasman et al., 1996; Pietrzak et al., 2017; Popp et al., 2015; Umegaki et al., 2000; Weiner et al., 1997).

Evidence from both preclinical and clinical studies suggests aerobic exercise may prevent age-related declines in cognitive performance and decrease cardiovascular risk factors (Lytle et al., 2004; Oliff et al., 1998; Schuit et al., 2001; Sherman et al., 1985; Singh-Manoux et al., 2005; van Gelder et al., 2004; van Praag et al., 1999, 2005; Voss et al., 2013). Increasing cerebrovascular health through reduction in cardiovascular risk factors may promote healthy brain aging twofold. First, better cerebrovascular reactivity predicts less cognitive decline from Alzheimer's disease (Benedictus et al., 2017; Leeuwis et al., 2017; Mielke et al., 2007; Silvestrini et al., 2006). Secondly, voluntary exercise attenuates age-related declines in memory performance in both rodents and humans (Heaney et al., 2013). Alterations in the hypothalamic-pituitary-adrenal axis may be the mechanism driving the beneficial effects that aerobic exercise has on the brain (Phillips et al., 2007). In healthy older adults, aerobic capacity (VO_2max) was positively correlated with both hippocampal volume (Erickson et al., 2011) and cognitive performance (Brown et al., 2010). In individuals with probable early Alzheimer's disease, cardiorespiratory fitness has been positively associated with memory and executive function and positively associated with whole brain and white matter volume (Burns et al., 2008). Aerobic exercise is one of the most widely studied mechanisms for increasing aerobic capacity and cardiorespiratory fitness, particularly in relation to cognitive aging (Brown et al., 2010; Colcombe et al., 2004; Erickson et al., 2009; Heath et al., 2016; Hillman et al., 2008; Hsu et al., 2018).

Salivary and blood cortisol levels increase shortly after exercise in adult males and are positively related to the duration and intensity of activity (Gatti and De Palo, 2011; Jacks et al., 2002; Tremblay et al., 2005). In older adults, individuals with highstress levels who engaged in exercise had a better (i.e., lower) ratio of cortisol to dehydroepiandrosterone (DHEA) when compared to equally stressed, sedentary older adults (Heaney et al., 2013). DHEA has a role in balancing the HPA and has been linked with both physiological and psychological health (Heaney et al., 2013). As such, a lower ratio of cortisol to DHEA is considered to be a healthier balance for the HPA (Heaney et al., 2013). These data suggest that engaging in long-term exercise may prevent potentially harmful age-related flattening in CAR. In other words, functional improvement of HPA axis function may be one mechanism by which aerobic exercise attenuates age-related cognitive decline. Acute cortisol has been used as a biomarker of both resistance exercise response (Hakkinen and Pakarinen, 1995; Kraemer et al., 1998) and aerobic exercise response (Luger et al., 1987); however, as discussed above, CAR is a better representation of HPA function when compared to single time points or 24-hour cortisol collection (Fries et al., 2009; Hellhammer et al., 2007; Kirschbaum and Hellhammer, 1994).

Alterations in HPA function and exercise are related to subjective stress. Meta-analyses have concluded that, following acute aerobic exercise, there is a consistent increase in salivary cortisol levels (Hayes et al., 2015; Heijnen et al., 2015). In addition, cardiorespiratory fitness was shown to attenuate cortisol response to a laboratory stressor (Zschucke et al., 2015). However, the majority of this work has been completed in young men (Budde et al., 2015), which might not generalize well to an aging population. There are limited data investigating the acute effects of exercise on cortisol or perceived stress in older adults. In older men, cortisol levels increased following an acute high-intensity sprint and strength training session but were only significantly increased in the control group compared to those who were trained (Sellami et al., 2017). Intensity of exercise is relevant to improving perceived stress in older adults, with low to moderate intensity exercise not being sufficient to improve perceived stress in midlife women (Nigdelis et al., 2018). However, a 6-month moderate to vigorous exercise intervention was shown to be effective in reducing distress and improving overall Quality of Life in older adults (Awick et al., 2017).

Exercise has been shown to have a beneficial effect on depression in a large meta-analysis, with a moderate clinical effect (Cooney et al., 2013; Krogh et al., 2011). In older adults, aerobic exercise has similar efficacy to more traditional treatments such as medications or therapy (Moore and Blumenthal, 1998). In a population based study of old adults, inactive individuals endorsed more depressive symptoms compared to those who engaged in either light or vigorous exercise (Lindwall et al., 2007). There is also evidence that exercise can have an anxiolytic effect in otherwise healthy adults (Strohle, 2009). Finally, there is a hypothesis that suggests that there is a shared mechanism for the improvement in cognition and mood symptoms seen with exercise, and increases in brain derived neurotrophic factor (BDNF) levels (Erickson et al., 2012). Exercise-related effects of BDNF are seen primarily within the hippocampus, a brain structure involved in both memory and the regulation of the HPA axis (Erickson et al., 2012).

The primary aim of this research was to determine if there are changes in the CAR or cortisol daily AUC after a 6-month aerobic exercise intervention in sedentary, but otherwise healthy older adults. It was predicted that the CAR would be more robust after the intervention. The secondary aim of this research was to determine if changes in the CAR after the 6-month aerobic exercise intervention were associated with changes in cognitive performance. It was hypothesized that changes in the magnitude of the CAR would be positively associated with exercise-related changes in cognitive performance. Finally, this study had an exploratory aim to investigate the relationship between changes in the CAR and psychological outcomes (i.e. depressive and anxiety symptoms, and subjective stress) across the exercise intervention.

2. Methods

2.1. Participants

This investigation was completed as an ancillary study of the larger Brain in Motion (BIM) study which was designed to investigate the effect of an aerobic exercise intervention on cognition in a population of healthy, sedentary older adults. The parent study includes 206 participants who completed the 6-month aerobic exercise intervention. Previous studies have shown the efficacy of a 6-month aerobic exercise intervention in improving cognitive performance (Heath et al., 2016; Radloff, 1977). All participants were generally healthy and screened for inclusion/exclusion criteria for the BIM study, for details please see Tyndall et al. (2013). The ancillary study began recruitment in the final

Table 1
Participant Demographics by Sex.

Variables	Sex			
	Women (n = 23)		Men (n = 15)	
	M	SD	M	SD
Age	63.90	4.93	66.74	4.95
Education	15.70	2.14	17.43	3.72
Montreal Cognitive Assessment	27.87	1.60	27.07	1.34
Estimated IQ	111.13	5.23	110.43	6.48
Marital Status (% Currently Married)	65.2%		100%	
Baseline Cognitive Domain Z-Scores				
Total Cognition	.18	.38	.06	.50
Verbal Memory	.42	.81	.01	.89
Verbal Fluency	.24	.60	−.21	.91
Figural Memory	−.01	1.02	.20	1.04
Executive Processing Speed	.12	.60	.11	.61
Executive Concept Formation	.36	.93	.24	.68
Complex Attention	−.04	.20	.04	.19

Note: No significant differences in demographics were observed between sexes.

18-months of the parent study and based upon enrollment dates, up to 58 participants were approached. A total of thirty-eight participants were recruited from the parent study (Table 1; Mean age = 65.0; 60% female) at their baseline visits and completed a separate consent procedure. Across the study, a total of six participants were lost: four dropped out from the study, one participant did not follow instructions for data collection and one participant was lost to follow-up, leaving a final sample of 32 participants. In addition, at follow-up four participants completed saliva sampling procedures but had missing data in their questionnaires, leaving 27 participants with longitudinal (baseline and follow-up) psychological data. Participants completed all measures at baseline, and again after a 6-month aerobic exercise intervention. The supervised exercise intervention was titrated, for each participant to reach 60–70% of their maximum heart rate reserve, three days a week. For more information on the intervention please see (Tyndall et al., 2013). All measures were collected ± 7 days from each other.

2.2. Cortisol profiles

Participants were instructed on salivary cortisol sampling at their first visit and take-home instruction sheets were provided. At each sample collection time, participants were asked to refrain from: 1) alcohol on the night before and during the saliva collection; 2) consuming food and drink (except water as necessary) for one hour before each sample; 3) brushing teeth one hour before each sample; and 4) completing collection on a day when they participated in their study exercise. On the collection day, participants were asked to provide small (1 ml) passive drool samples at the following points: waking, 15, 30, and 45 min post-waking and 3, 6, 9, and 12 h post-waking, according to standard procedures and using standard calculations for both CAR and total cortisol (Edwards et al., 2001b; Stalder et al., 2016). Graphical representation of each parameter can be seen in Fig. 1. Saliva was collected in sterile Nalgene cryovials and stored in participant's freezers until returned to the study. Samples were transported to the laboratory in a cooler provided to the participant. Total daily area under the curve (AUC_d), and Morning AUC (AUCi) were calculated with respect to nadir (i.e. lowest value) for each participant. Morning AUC_i was the primary CAR outcome (Stalder et al., 2016). We did not use the AUC with respect to ground, as a true zero value is not physiologically relevant (Stalder et al., 2016). Time of peak cortisol was also calculated (Fig. 1).

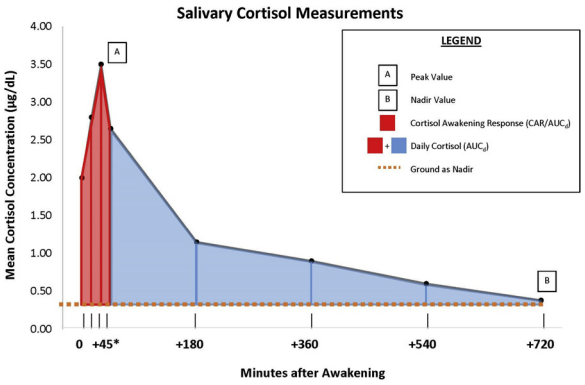

Fig. 1. Cortisol awakening response calculated variables.
Peak value of cortisol was the highest cortisol value measured across the 8 sampling time points. **Nadir Value** was the lowest cortisol value measured across the 8 sampling time points. **Morning Area under the curve** to nadir (Morning AUC_i/ CAR) was defined as the cortisol awakening response (CAR) in this protocol. **Total area under the curve** (Total AUC_d) was defined as daily cortisol.

2.3. Cortisol sample preparation and quantification

Samples were prepared and a protein precipitation solution was produced by mixing ZnSO4•7H2O solution (9 mg/mL) with the deuterated cortisol internal standard (IS). Saliva was centrifuged for 10 min and then 75 µL of saliva was transferred into a 0.5 mL micro-centrifuge tube, followed by adding 75 µL of protein precipitation solution. The mixture was vortexed for 30 s before being incubated at -20 °C. After 30 min, the sample was centrifuged at 14,000 rpm for 15 min. 120 µL of supernatant was submitted to LC–MS analysis. Since LC–MS is relying upon mass-to-charge ratio, there is little to no false positive identification in this technique (Miller et al., 2013).

2.4. LC–MS analysis

All samples were analyzed by using an Agilent 1200 binary liquid chromatography (LC) system coupled to an AB SCIEX QTRAP 5500 tandem mass spectrometer equipped with an atmospheric pressure chemical ionization (APCI) source. The LC separation was performed by Agilent Poroshell 120 C18 column (50 x 3 mm, 2.7 µm particle size) at 45 °C. Mobile phase A was H2O/MeOH (75/25, v/v) and mobile phase B was MeOH/IPA (90/10, v/v). 8.5 min gradient was 20–40% B (0–1.0 min), 40–60% B (1.0–5.0 min), 60–100% B (5.0–5.5 min), 100% B (5.5–6.5 min), 100-20% B (6.5–7.0 min), and held at 20% B (7.0–8.5 min). The flow rate was 0.6 mL/min and the injection volume was 20 µL. Cortisol was ionized under positive APCI mode. LC–MS data were acquired via multiple reaction monitoring (MRM). Cortisol was monitored by two transitions (a quantifier and a qualifier). Mass resolutions in Q1 and Q3 were set to unit resolution.

2.5. Chemicals and reagents

Cortisol was purchased from Steroids Inc (Newport, RI). Deuterium-labeled internal standards: cortisol-9,11,12,12-d4 (cortisol-d4) was obtained from CDN Isotopes Inc (Pointe-Claire, Quebec, Canada). ZnSO4•7H2O was purchased from EMD Chemicals Inc (Darmstadt, Germany). Optima grade methanol and water were purchased from Fisher Scientific (Edmonton, Canada). MS nitrogen was provided by a Parker Source5000 nitrogen generator (Ohio, USA).

2.6. Cognitive assessment

Current cognitive performance was assessed using a standardized neuropsychological test battery, administered by trained study

Table 2
Participant baseline cognitive performance.

Variables	Overall		Sex			
			Women (n = 23)		Men (n = 15)	
	M	SD	*M*	SD	*M*	SD
Verbal Memory - Selective Reminding						
Immediate Recall	48.5	7.0	50.1	6.6	46.0	7.1
Delay Recall	8.0	2.1	8.4	1.9	7.3	2.4
Cued Recall	9.0	1.8	9.3	1.7	8.7	2.0
Verbal Fluency - DKEF						
Letter Fluency	44.4	9.9	46.2	8.5	41.6	11.5
*Category Fluency**	42.1	6.9	44.3	5.7	38.6	7.3
Category Switching	14.3	2.3	14.7	1.8	13.6	2.9
Figural Memory - MCG						
Immediate Recall	28.6	5.6	27.8	4.7	29.7	6.6
Delay Recall	28.0	5.4	27.6	5.2	28.5	5.7
Executive Function: Concept Formation DKEF						
Card Sorting - # Correct Sorts	5.0	1.4	5.3	1.1	4.6	1.7
Card Sorting - Recognition	17.4	5.6	17.7	4.6	16.9	7.0
*Card Sorting - Free Sort**	19.2	5.8	20.7	4.5	16.8	6.8
Executive Processing Speed						
Digit Symbol -Oral	56.6	7.1	57.3	7.1	55.5	7.2
Digit Symbol -Written	48.9	6.3	48.7	6.9	49.1	6.3
Color Word - Color Reading	32.2	5.3	33.0	5.6	31.1	4.8
Color Word - Word Reading	24.2	4.3	24.1	3.9	24.5	4.9
Color Word - Inhibition	63.2	12.2	64.9	12.6	60.5	11.5
Color Word - Switching	63.7	11.8	63.7	10.1	63.9	14.5
Complex Attention						
Auditory Consonant Trigrams	48.9	6.1	48.1	5.6	50.3	6.8

Note. Notations indicate significant differences observed between men and women. * p < .05, **p < .01, *** p < .001. DKEF = Delis-Kaplan Executive Function; MCG = Medical College of Georgia Complex Figure.

personnel at the University of Calgary. The cognitive test battery lasted about 2.5 h and was designed to assess seven main cognitive domains including: Executive Processing Speed, Executive Function, Concept Formation, Verbal Fluency, Figural Memory, Verbal Memory, Complex Attention, and Total Cognition. Raw test scores were converted to z-scores normalized to baseline performance and averaged for each domain, as well as averaged overall for a total cognitive domain score (Table 1.). Baseline raw neuropsychological test scores for the overall group, and by sex are reported in Table 2. The testing battery consisted of the following tests: 1) Buschke Selective Reminding Test; 2) Medical College of Georgia Complex Figure Test; 3) Symbol Digit Modalities Test; 4) Auditory Consonant Trigrams; 5) Delis-Kaplan Executive Function Card Sorting Test; 6) Delis-Kaplan Executive Function Color Naming Test; and 7) Delis-Kaplan Executive Function Verbal Fluency Test. Estimated IQ was determined using the North American Adult Reading Test (Uttl, 2002).

2.7. Psychological outcomes

Current psychological state was assessed using a series of self- administered questionnaires which were to be completed the day of cortisol sampling. Depressive symptoms were assessed using the Center for Epidemiological Studies, Depression Scale (CES-D) (Radloff, 1977). Anxiety symptoms were assessed using the Beck Anxiety Inventory (BAI) (Wilson et al., 1999), and anxiety sensitivity was assessed using the Anxiety Sensitivity Index (ASI) (Peterson and Heilbronner, 1987). Subjective stress levels were assessed using the Perceived Stress Scale (PSS) (Cohen et al., 1983).

2.8. Data analyses

All statistical analyses were completed using either SPSS 24.0 (Chicago, IL) or JASP 8.1.2. All data were checked for outliers and normality before analyses were initiated. To test if there were differences between the CAR before and after the exercise intervention, we utilized a Bayesian repeated measures analysis of covariance (ANCOVA) with 2 (Intervention: Baseline, Post-Exercise) x 8 (Time: Wake, +15 min; +30 min, +45 min, +3Hrs, +6Hrs, +9Hrs, +12Hrs) design. To determine if either Morning (AUC_I) or AUC_d changed across the aerobic exercise intervention, analysis of covariance (ANCOVA) was used, controlling for age and sex.

Finally, to determine the relationship between cortisol levels and cognitive performance, a series of linear regressions were used. Controlling for age, sex and estimated IQ, cortisol AUC_d and CAR were used as predictors of cognitive performance in stepwise regression equations. In addition, in a separate set of regressions, psychological outcomes (i.e. CESD and PSS scores) were used to predict cortisol outcomes. To decrease the likelihood of Type II error, only *a priori* relevant cognitive domains (verbal, attention and memory domains), and total cognitive performance were analyzed when investigating change across the intervention. Each domain was analyzed in a separate regression model.

3. Results

3.1. Effects of the exercise intervention on the CAR

Main effects of Time (BF10 = 2.929e +34; Posterior Probability > 99%) and Intervention (BF10 = 3.462; Posterior Probability = 77.59%) were observed. In contrast to previous studies, we did not observe main effects of age or sex, and no significant interactions were observed. As expected, there was a strong circadian effect on cortisol concentrations. Using Bayesian inference, there is a 77.6% likelihood of observing a change in the shape of the CAR after the exercise intervention again (Fig. 2). There was also a significant increase in CAR (t(26) = -3.56, p = .001), but not AUC_d (t(26) = 0.38, p = .71) from pre- to post- intervention (Fig. 3).

3.2. Cortisol is related to cognitive performance at baseline, but not post-intervention

As expected, we saw the strongest relationships between verbal outcomes and cortisol. Morning cortisol AUC_i was negatively related to verbal memory (r(33) = -0.34, p = .047) and verbal fluency (r(33) = -.40, p = .019) performance at baseline. Complex attention

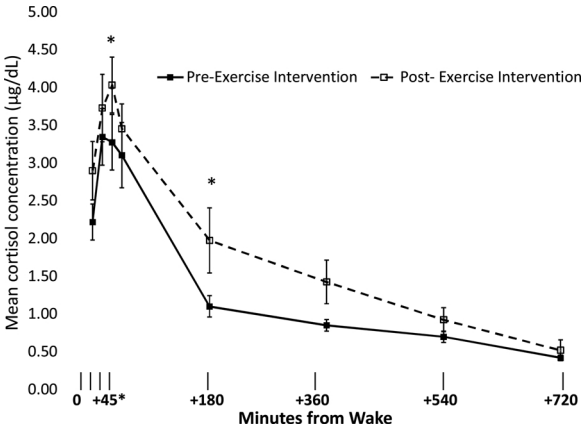

Fig. 2. Cortisol awakening response across BIM Study.
The Cortisol Awakening Responses (CAR) is significantly increased after the exercise intervention. Time points at 30 min, and 5 h after awakening have the greatest effect. Using Bayesian inference, there is a 77.59% likelihood of the effect of observing a change in the shape of the CAR again, after a similar exercise intervention. Error Bars = +/- 1 S.E.M.

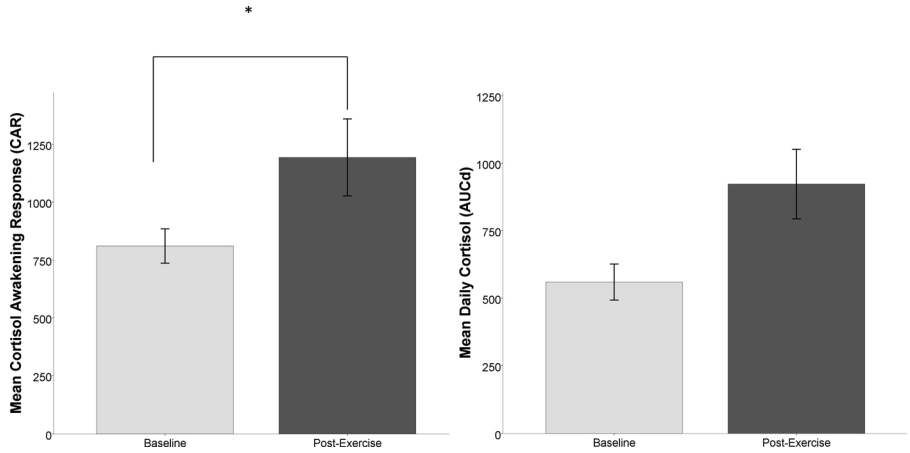

Fig. 3. Change in Cortiol Area under the Curve after a 6-month exercise intervention in healthy older adults.
There was a significant increase in Cortisol Awakening response (CAR/AUC_i) from pre- to post-intervention (p = .001), but this change was not observed in AUC_d (p = .71). Error Bars = +/- 1 S.E.M.

performance was positively associated with baseline AUC_d (r(33) = .37, p = .032). There were no significant relationships between performance on other cognitive domains, so these were not included in subsequent regression analyses.

We did not find any relationship between cortisol outcome measures and total cognition. Specifically, morning cortisol AUC_i (β = -0.16, p = 0.30) or cortisol AUC_d (β = -0.15, p = 0.34) did not predict total cognition at baseline. We also did not observe that total cognition was predicted by morning cortisol AUC_i (β = -0.07, p = 0.70) or cortisol AUC_d (β = 0.06, p = 0.7) post-intervention. Cortisol AUC_d (β = -0.35, p = 0.04) and morning cortisol AUC_i (β = -0.36, p = 0.03) were negatively related to verbal fluency at baseline, but these relationships did not hold post-intervention. Similarly, baseline cortisol AUC_d (β = 0.45, p = 0.01) was related to complex attention, with no significant relationship with morning cortisol AUC_i (β = 0.32, p = 0.07). These associations were not seen post-intervention.

3.3. Change in cortisol AUC_i does not predict change in cognition

Contrary to expectations, there were no significant correlations between change in CAR across the intervention and change in cognitive performance. However, there was a negative association between change in AUC_d and figural memory performance (r(26) = -0.36, p = .036). To further confirm the null effects, we conducted a series of regression analysis to determine if, after controlling for age, sex, and educational attainment, there would be an association between cortisol profiles and total cognition. The analyses again confirmed there was no relationship between change in total cognition across the intervention and CAR (β = -0.07, p = 0.72), or AUC_d (β = -0.14, p = 0.47). With the addition of covariates, figural memory performance across the intervention was no longer predicted by change in CAR (β = -0.15, p = 0.48), or cortisol AUC_d (β = -0.34, p = 0.11) (Fig. 4).

3.4. Changes in psychological outcomes relate to changes in cortisol profiles

Previous research has suggested that perceived stress relates to the cortisol awakening response. We undertook an exploratory analysis to identify if the changes in perceived stress and depressive symptoms across the intervention were related to observed changes in cortisol. Post intervention, depressive symptoms, as measured by the CES-D, were significantly and positively related to AUC_d (r(26) = .45, p = .023). In addition, changes in perceived stress across the intervention was positively related to change in both AUC_d (r(25) = .47, p = .017) and CAR (r(25) = .52, p = .008). To further explore this relationship, change in perceived stress was used as a covariate in the regression models predicting change in both AUC_d and CAR. When controlling for age and sex, a greater reduction in perceived stress was a strong positive predictor of increase in both AUC_d (β = 0.76, p < .000) and CAR (β = 0.81, p < .000).

4. Discussion

Utilizing the current study's comprehensive set of salivary cortisol data in a small sample population of healthy older adults, a robust cortisol awakening response, and increased CAR after exercise, were observed. These data provide support for the current study's hypothesis that aerobic exercise is a potential mechanism for improving HPA axis function in otherwise healthy older adults. However, the second hypothesis, that changes in the cortisol awakening response across the exercise intervention would be related to improved cognitive performance, was not supported. Finally, exploratory analyses confirmed that improvements in CAR across the intervention were positively associated with decreases in perceived stress. However, this effect was independent of changes in cognition across the trial. In addition, neither baseline perceived stress, nor perceived stress predicted change in the CAR, suggesting the changes in psychological outcomes were independent of baseline psychological health.

Within the current research, we did not observe an association between the primary measure of CAR (cortisol AUC_i) and function in expected cognitive domains, including verbal and memory outcomes (Comijs et al., 2010; MacLullich et al., 2005). Across aging, increases in cortisol secretion are observed in both preclinical (Issa et al., 1990) and clinical studies (Halbreich et al., 1984; Sherman et al., 1985). Previously, higher cortisol levels in aging have been linked with poorer cognitive performance and hippocampal atrophy (Lupien et al., 1994, 1998). In the Age, Gene/Environment Susceptibility (AGES)–Reykjavik Study (Geerlings et al., 2015), healthy older adults higher morning cortisol levels were associated with better processing speed and executive function. However, higher cortisol levels are not always associated with improved cognition. Within these same adults, elevated evening cortisol levels have been associated with impairments in memory, processing speed, and executive function performance and with decreased grey matter volume (Geerlings et al., 2015). Although not a specific aim of the current study, we did not see any significant associations between sample 1 (taken at awakening) or the last evening salivary cortisol and cognitive function. This may be due to differences in collection times between studies. In this study, the last sample was taken 12 h after awakening; however, in the AGES- Reykjavik Study the bedtime sample was taken shortly before participants were going to sleep for the night. It is also of note, that single sample cortisol

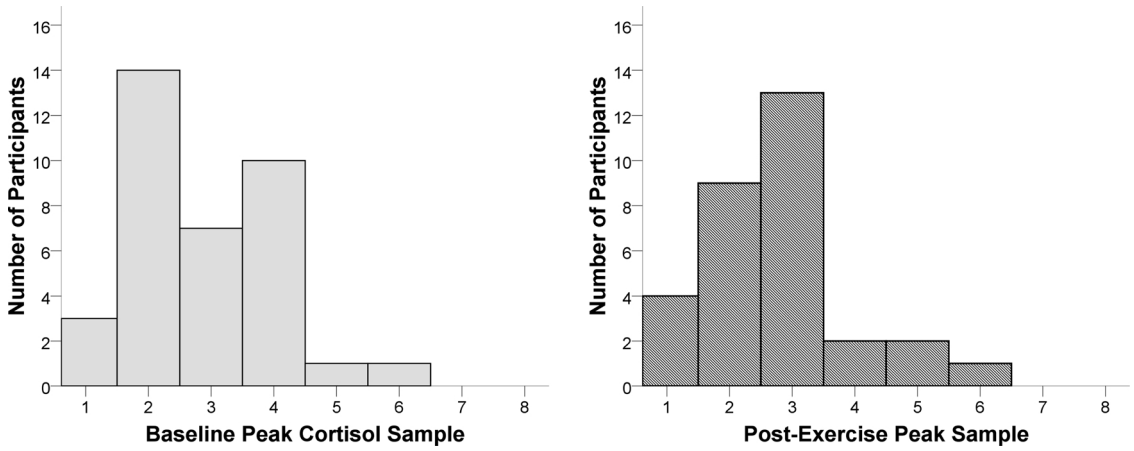

Fig. 4. Number of Participants with a peak sample at each time point.
The distribution of the time point at which participants were having their peak cortisol level shifted from pre- to post-intervention.

measurements of cortisol reactivity, as in the (AGES)–Reykjavik Study, are not measuring the same construct as the CAR (Clow et al., 2004). Therefore, it is unsurprising the results differ. However, no other research has been conducted on changes in the CAR with exercise and cognition in healthy older adults.

Exercise may have a stress-buffering effect through cross stressor adaptation, meaning long-term exercise may decrease acute HPA reactivity to psychological and physiological stressors (Zschucke et al., 2015). There is evidence that habitual exercise decreases response to lab stressors in trained young men. Three studies of highly-trained or elite athletes suggested that continued athletic activity reduced cortisol response to an in-lab stressor when compared to sedentary or untrained young men (Rimmele et al., 2009, 2007; Zschucke et al., 2015). However, acute stress reactivity and basal cortisol levels are often disassociated (Kidd et al., 2014). The CAR is not associated with afternoon levels or cortisol across the day (Edwards et al., 2001a). In addition, there is limited generalizability of a study in young men to an aging population. Aging is often associated with increased time required to recover to homeostasis, and increased circulating cortisol. However, exercise may improve or maintain sensitivity to the HPA negative feedback circuit by providing input into the system (Traustadottir et al., 2004). In a small study of older adults with mild cognitive impairment, there was a greater difference in peak to nadir cortisol in those who completed a 3-month exercise intervention compared to controls (Baker et al., 2010).

Exercise may also have a positive effect on HPA reactivity through mediation of subjective stress. The current study suggests that there is a positive relationship between daily cortisol (AUC_d) and subjective stress. A previous observational study in older adults reported a similar direction of findings, with a poorer (i.e. higher) cortisol:DHEA ratio in those who reported higher stress severity and did not engage in physical exercise (Heaney et al., 2013). Engaging in at least one hour of aerobic exercise a week mitigated these effects (Heaney et al., 2013). Exercise attenuates stress reactivity and subjective stress ratings to an in-lab stressor in young men who were randomized to 30 min of acute moderate exercise, compared to those who engaged in a placebo exercise bout (Zschucke et al., 2015). Additionally, across both treatment groups, men with higher aerobic fitness (VO_2max) had lower cortisol responses to the stressor (Zschucke et al., 2015).

To our knowledge, this is the first study looking at the effect of an exercise intervention on CAR, specifically within the context of cognitive functioning in healthy older adults. However, there are some weaknesses in the design. This is a semi-experimental study design, as there is no comparison control group. This is of particular importance, as improving cognitive performance in adults through an intervention is very difficult. Often, not seeing declines in cognitive performance is seen as a positive outcome in cognitive intervention studies (Goh et al., 2012; Nyberg et al., 2012), which is most apparent when a control group is used. In addition, while the CAR sampling was completed in close timing to the cognitive assessment, they were not completed on the same day. Day-of measurements of CAR may be more closely related to cognitive performance. Time of administration of the cognitive assessments was not the same for all participants due to scheduling limitations. However, our sample size was limited so it remains possible that other associations would emerge in a larger trial. Future work should include a larger sample size, and include factors like diet and sleep as potential mediators of the effects of exercise on CAR. Despite these methodological shortcomings, this design has a few key strengths. First, this is a within-subject design, which increases the likelihood of seeing small effects. In addition, a gold-standard protocol was used for assessing the CAR (Stalder et al., 2016), and additional afternoon and evening samples were collected to assess basal cortisol levels.

Future studies are needed to assess the role CAR may play as a mechanism for cognitive decline across aging. Specifically, future studies should include a control group. In addition, it would be informative to include individuals who are at risk for CAR dysfunction including those with a history of major depression, have genetic risk factors for developing dementia (i.e., Apolipoprotein allele ε4), and dementia caregivers (Wahbeh et al., 2008). In addition, this study suggests that 6 months of aerobic exercise is sufficient to have a positive effect on the CAR. However, this change was not related to changes in cognitive performance. Changes in CAR may still be a mechanism for positive changes in mood and cognition. However, it may also be mediated by improvements in general health, or other risk factors like hypertension or diabetes.

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Conflicts of interest

No authors report any conflicts of interest.

CRediT authorship contribution statement

Lauren L. Drogos: Conceptualization, Formal analysis, Investigation, Writing - original draft, Visualization, Data curation, Funding acquisition. **Katherine Wynne-Edwards:** Methodology, Resources, Visualization, Formal analysis, Writing - review & editing, Supervision, Project administration. **Ruokun Zhou:** Methodology, Investigation, Writing - review & editing. **Samantha E. Hall:** Investigation, Writing - review & editing. **Amanda V. Tyndall:** Investigation, Writing - review & editing. **R. Stewart Longman:** Conceptualization, Methodology, Writing - review & editing. **Gail Eskes:** Conceptualization, Methodology, Writing - review & editing. **Marc J. Poulin:** Conceptualization, Methodology, Resources, Formal analysis, Visualization, Writing - review & editing, Data curation, Supervision, Funding acquisition, Project administration.

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