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Association between Lifetime Physical Activity and Cognitive Functioning in Middle-Aged and Older Community Dwelling Adults: Results from the *Brain in Motion* Study

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Abstract

To determine if total lifetime physical activity (PA) is associated with better cognitive functioning with aging and if cerebrovascular function mediates this association. A sample of 226 (52.2% female) community dwelling middle-aged and older adults (66.5 ± 6.4 years) in the *Brain in Motion* Study, completed the *Lifetime Total Physical Activity Questionnaire* and underwent neuropsychological and cerebrovascular blood flow testing. Multiple robust linear regressions were used to model the associations between lifetime PA and global cognition after adjusting for age, sex, North American Adult Reading Test results (i.e., an estimate of premorbid intellectual ability), maximal aerobic capacity, body mass index and interactions between age, sex, and lifetime PA. Mediation analysis assessed the effect of cerebrovascular measures on the association between lifetime PA and global cognition. *Post hoc* analyses assessed past year PA and current fitness levels relation to global cognition and cerebrovascular measures. Better global cognitive performance was associated with higher lifetime PA ($p = .045$), recreational PA ($p = .021$), and vigorous intensity PA ($p = .004$), PA between the ages of 0 and 20 years ($p = .036$), and between the ages of 21 and 35 years ($p < .0001$). Cerebrovascular measures did not mediate the association between PA and global cognition scores ($p > .5$), but partially mediated the relation between current fitness and global cognition. This study revealed significant associations between higher levels of PA (i.e., total lifetime, recreational, vigorous PA, and past year) and better cognitive function in later life. Current fitness levels relation to cognitive function may be partially mediated through current cerebrovascular function. (*JINS*, 2015, *21*, 816–830)

Keywords: Humans, Aging, Exercise, Prevention, Cerebrovascular Function, Questionnaires

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INTRODUCTION

Normal aging may result in structural and functional modifications to the brain, such as a reduction in brain volume (Good et al., 2001; Peelle, Cusack, & Henson, 2012), decline

in resting cerebral blood flow (CBF) (Brown et al., 2010; Zimmerman et al., 2014), and cerebrovascular reactivity (Barnes, Taylor, Kluck, Johnson, & Joyner, 2013; Brown et al., 2010). These changes in cerebrovascular health and cell integrity have been associated with an increased risk of stroke (Gupta et al., 2012), premature mortality (Portegies, de Bruijn, Hofman, Koudstaal, & Ikram, 2014; Sabayan et al., 2013), Alzheimer's disease and related dementias (Amieva et al., 2005; Lautenschlager, Cox, & Cyarto, 2012), and declining cognitive function (Davenport, Hogan, Eskes, Longman, & Poulin, 2012; Matteis, Troisi, Monaldo, Caltagirone, & Silvestrini, 1998). Physical activity (PA) has been identified as one of the most promising modifiable lifestyle factors for improving cerebrovascular health (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010; Chapman et al., 2013; Prakash, Voss, Erickson, & Kramer, 2015; Tarumi et al., 2013) and preventing age-associated cognitive decline (Abbott et al., 2004; Buchman et al., 2012; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Rovio et al., 2005; Scarmeas et al., 2009; Tarumi et al., 2013). Furthermore, the benefits of PA include increased cerebrovascular function (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010; Burdette et al., 2010; Chapman et al., 2013; Davenport et al., 2012), decreased risk of cerebrovascular and cardiovascular diseases (Qiu & Fratiglioni, 2015) and a decreased risk of Alzheimer's disease and related dementias (de Bruijn et al., 2013; Nation et al., 2013; Rovio et al., 2005).

Previous research indicates that older adults who engage in more physically active recreational activities or have higher cardiovascular fitness are at lower risk for cognitive decline compared to inactive older adults (Blondell, Hammersley-Mather, & Veerman, 2014; Colcombe et al., 2004; Forbes, Thiessen, Blake, Forbes, & Forbes, 2013; Kramer et al., 1999; Prakash et al., 2015, 2011). Attention has been focused on the effects of current leisure time or recreational PA on cognitive function, demonstrating the potential importance of remaining active in older age (Rovio et al., 2005; Weuve et al., 2004; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). For example, in females ≥65 years, walking more than three times per week was associated with a decreased risk of cognitive decline (Yaffe et al., 2001). Rovio et al. (2005) demonstrated that leisure-time PA in midlife (age 44–57 years) is associated with a decreased risk of dementia in late life, while Verghese et al. (2003) showed increased participation in leisure activities for individuals ≥75 years old reduced the risk of developing dementia and Alzheimer's disease.

Physical activity can be measured using metabolic equivalents (METs). A MET is defined as the ratio of the associated metabolic rate for an activity compared to the resting metabolic rate. One MET is equivalent to the amount of oxygen that is metabolized while at rest in a seated position, and is approximately 3.5 mL/kg/min of oxygen consumption ($\dot{V}O_2$; normalized to body mass) (Jette, Sidney, & Blumchen, 1990). With increasing intensity of PA, the MET value increases; for example, a 3 MET activity is achieved by walking at 2.5 miles per hour on a flat firm surface, while cross country hiking is rated as a 6 MET activity (Ainsworth et al., 2011). It has been demonstrated that increasing MET-hr/week spent in recreational and household activities over the past 2 weeks is associated with a lower risk of dementia (de Bruijn et al., 2013), and increasing MET-hr/week of leisure time PA over the past year resulted in increased mean cognitive scores (Weuve et al., 2004).

Cerebrovascular health and function can be measured using indices of resting CBF and cerebrovascular reactivity. Cerebrovascular reactivity is the magnitude of change in CBF for a given stimulus [e.g., increased partial pressure of CO_2 (PCO_2)], with enhanced vascular reactivity thought to represent better cerebrovascular function and health (Brown et al., 2010; Davenport et al., 2012). Previous research provides evidence suggesting that increased levels of PA or cardiovascular fitness are associated with improved cerebrovascular functioning (Ainslie et al., 2008; Bailey et al., 2013; Burdette et al., 2010), with additional studies indicating that cerebrovascular functioning is also associated with improved neurocognitive function within the same sample (Brown et al., 2010; Chapman et al., 2013; Tarumi et al., 2013). Reduced cerebrovascular functioning has been proposed as a mechanism underlying cognitive and cerebrovascular dysfunction (Davenport et al., 2012). Recently it has been shown that indices of cerebrovascular function mediate the relation between PA and cognition in healthy young adults providing support for the hypothesis that cerebrovascular health is a plausible pathway linking frequent PA and improved cognitive status (Guiney, Lucas, Cotter, & Machado, 2015). Specifically, more frequent PA was associated with enhanced cognitive control and this relationship was mediated by cerebrovascular reactivity to PCO_2, as per statistical mediation analysis (Guiney et al., 2015). Together these studies suggest that cardiovascular and cerebrovascular health may contribute to better cognitive functioning.

Dysfunction in both cognitive performance (Andel et al., 2008; Rovio et al., 2005; Yaffe et al., 2001) and cerebrovascular functioning (Tarumi et al., 2013) can begin in midlife (i.e., ~40–60 years old) rather than exclusively in old age (Kareholt, Lennartsson, Gatz, & Parker, 2011). Previous research has highlighted the need for additional investigations addressing the influence of PA on cognitive abilities throughout the lifespan to complement current work that focuses attention on periods more proximate to the onset of disease. Our study addresses this knowledge gap regarding the effects of lifetime total PA on cognitive and cerebrovascular outcomes in mid to later life while examining potential sex differences in these outcomes. Sex differences were considered as there is evidence suggesting that males and females have different physiological responses to PA (Brown, Peiffer, & Martins, 2013; Colcombe & Kramer, 2003; Ho, Woo, Sham, Chan, & Yu, 2001; Laurin et al., 2001). A variety of mixed sex studies have found that exercise positively impacts both sexes; however, the effects of increased exercise on cognitive functioning seem to be more pronounced in women (Brown et al., 2013; Ho et al., 2001; Laurin et al., 2001). Additionally, when studying cognition in a mixed-sex study it is important to account for sex differences (Kimura, 2002; Kimura & Hampson, 1994).

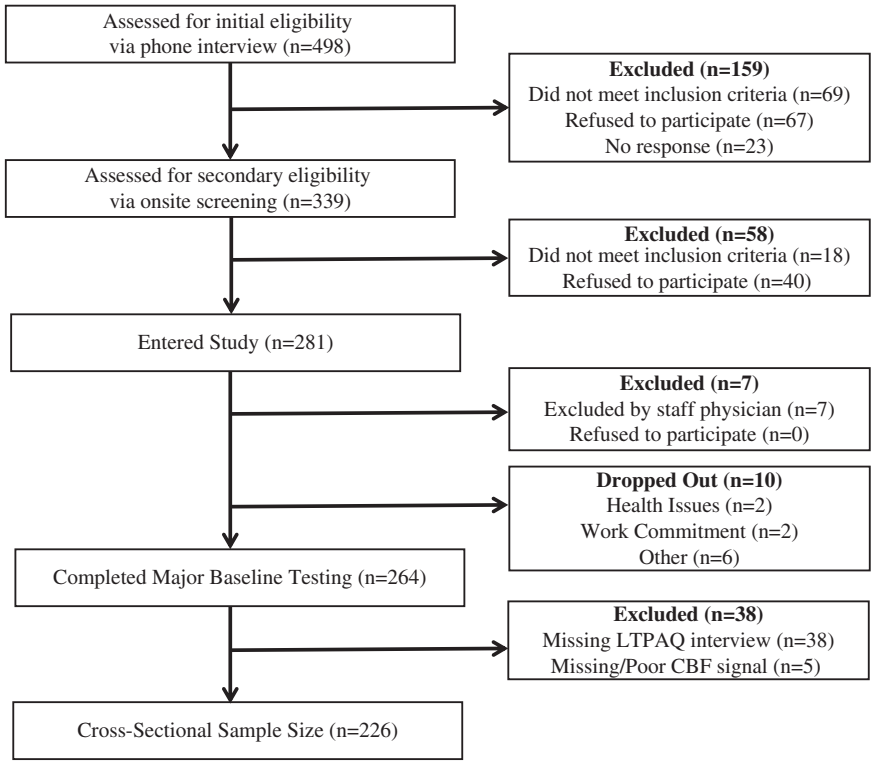

Fig. 1. Participant flow for the *Brain in Motion* Study, Calgary, Alberta, Canada.

This study tests the mediating effect of current cerebrovascular health on the relation between measures of lifetime PA and current cognitive functioning. We hypothesized that increased lifelong PA is associated with better global cognition and cerebrovascular function is associated with current cognitive performance, completing the proposed mediation relationship.

METHODS

Research Participants

The study population comprised participants in an ongoing intervention-cohort study on the effects of a 6-month aerobic exercise intervention on cerebrovascular regulation and cognitive function in middle-aged and older adults. The *Brain in Motion* study methods and protocol for the eligibility screening process has been previously described (Tyndall et al., 2013). Participants (n = 264) are healthy, community dwelling, currently inactive, middle-aged and older adults and were recruited through the use of media, posters and advertisements in local newspapers, communities, and through the University of Calgary. Eligibility criteria included: English speaking males or females ≥55 years old, considered currently inactive (<30 min of moderate exercise 4 days/week or 20 continuous min of vigorous exercise two days/week), able to walk independently outside and up and down at least 20 stairs, a body mass index (BMI) less than 35 kg/m^2 (to avoid co-morbidities associated with obesity), no history of clinically active cardiovascular disease or obstructive airway disease, non-smoker for the past 12 months, no major trauma or surgery in the last 6 months, no debilitating neurological disorders, physician clearance, and written informed consent. A detailed flow of participants is provided in Figure 1. The sample consists of participants who completed the *Lifetime Total Physical Activity Questionnaire* (LTPAQ) in addition to the neuropsychological assessment, and the cerebrovascular blood flow test (n = 226) at baseline. The University of Calgary Conjoint Health Research Ethics Board approved all study procedures.

Assessment of Lifetime Physical Activity

Lifetime total PA was assessed using the interviewer-administered LTPAQ, a tool with demonstrated reliability (Friedenreich, Courneya, & Bryant, 1998). This questionnaire assesses occupational, transportation, household and recreational physical activities from childhood to time of interview. Additionally, the frequency, duration, and intensity of PA are also reported. Before the interview, participants received two recall calendars as memory aids to complete. An interviewer trained in cognitive interviewing techniques used the calendars to help facilitate recall of PA history.

Lifetime total PA was the main variable of interest for this study. Intensities were assessed in two ways: (1) by self-report as sedentary (only for occupational activity described as activities sitting down), light (activities done mainly standing that do not increase heart rate and cause no sweating), moderate (activities that cause heart rate to increase slightly and cause light sweating), and vigorous activity

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(activities that cause heart rate to increase substantially and cause heavy sweating) and (2) as assigned by the study staff. For the latter approach, a MET value for each reported activity was assigned based on the *Compendium of Physical Activities* (Ainsworth et al., 2011). The main predictor for these analyses was the average MET-hours per week per year of life (MET-hr/week/year) of lifetime PA estimated as the sum of occupational, transportation, household, and recreational activity done from childhood to time of LTPAQ. For this study, additional analyses by type of activity, intensity of activity (0–3 METs: low, 3–6 METs: moderate, and >6 METs: vigorous) and activity during different age period in life (ages <20, 21–35, 36–50, 51–65 years) were conducted.

Neuropsychological Assessment

This assessment consisted of a 2.5 hour neuropsychological test battery administered by trained staff. The test battery was composed of eleven tests assessing seven cognitive domains including verbal memory, figural memory, processing speed, executive functioning, complex attention, verbal knowledge, and spatial reasoning. The list of neuropsychological tests corresponding to these domains of cognitive activity are displayed in Supplementary Table 1, and a detailed description has been previously published (Tyndall et al., 2013). Seven cognitive domain scores were calculated by taking the average *Z*-score of all tests within each domain. The global cognition score is the sum of seven equally weighted domain *Z*-scores, used as the cognitive outcome for all analyses. At the time of the cognitive assessment, participants also completed the North American Adult Reading Test (NAART) as a measure of premorbid verbal intellectual ability (Blair & Spreen, 1989). The NAART is sensitive to education (both formal and informal) and insensitive to mild forms of cognitive impairment, making it a better covariate than formal education when assessing cognitive abilities (Uttl, 2002).

Assessment of Indices of Cerebrovascular Blood Flow

Participants underwent a 2-hour assessment administered by trained staff. Two hours before testing, participants fasted and refrained from exercising. Blood flow velocity of the middle cerebral artery (MCAv) was measured using a 2-MHz pulsed transcranial Doppler ultrasound system recording measurements at an optimal placement slightly above and in front of the right ear (Aaslid, Markwalder, & Nornes, 1982; Poulin, Liang, & Robbins, 1996; Poulin & Robbins, 1996). Peak MCAv, heart rate, beat-by-beat blood pressure measurements, and arterial O_2 saturation were measured continuously throughout the protocol. Dedicated software recorded the exhaled CO_2 and O_2 at the end of each breath (referred to as end-tidal P_{CO2} and P_{O2}) during 10 min of seated rest. Each participant had his/her nose occluded with a nose clip and breathed room air through a mouthpiece. A fine capillary line inserted in a port immediately distal to the mouthpiece and connected to a mass spectrometer measured the concentration of CO_2 and O_2 continuously at the mouth, and breath-by-breath values for end tidal CO_2 (PET_{CO2}) and O_2 (PET_{O2}) were determined. These end-tidal values were averaged over the 10 min of rest and were used to determine the desired PET_{CO2} and PET_{O2} to assess the cerebrovascular response to the changes in the pressure of CO_2, also referred to as euoxic hypercapnia testing. The euoxic hypercapnia test lasted 12 min and included two 3-min step increases in PET_{CO2} as previously described (Brown et al., 2010; Tyndall et al., 2013). Physiological responses were calculated as the mean responses over the final 30 s of each stage during the hypercapnic challenges. A more technical description of the testing protocol can be found in the supplementary material.

This protocol yielded four measures of cerebrovascular function for analysis, including peak velocity of blood moving through the MCA ($\overline{V}P$), cerebrovascular conductance (CVC; *MCAv/Mean Arterial Pressure*), $\overline{V}P$, and CVC reactivity during the hypercapnic challenge. Specifically $\overline{V}P$ reactivity was calculated as the change in $\overline{V}P$ divided by the change in PET_{CO2} from +1 to +8 mmHg, while CVC reactivity is the change in CVC divided by the change in PET_{CO2} from +1 to +8 mmHg. These measures are widely used in the cerebrovascular literature using transcranial Doppler ultrasound techniques (Aengevaeren, Claassen, Levine, & Zhang, 2013; Ainslie et al., 2008; Bailey et al., 2013; Barnes et al., 2013; Brown et al., 2010; Demirkaya, Uluc, Bek, & Vural, 2008; Murrell et al., 2013; Zhu et al., 2013).

Additional Measures

At baseline socio-demographic, health and lifestyle, maximal aerobic capacity ($\dot{V}O_2$ max), and anthropometric were obtained (Table 1). Health and lifestyle information was obtained through self-reported questionnaires and included mood, alcohol consumption, and dietary intake assessed with the Canadian Diet History Questionnaire I (DHQI) (Csizmadi et al., 2007); hypertensive status (based on resting blood pressure measures and medications reported); and smoking history. Maximal aerobic capacity was obtained using a motorized treadmill following the Bruce protocol (Paterson, Cunningham, Koval, & St Croix, 1999) described elsewhere (Tyndall et al., 2013). Anthropometric measures were taken by trained staff and included height, weight, BMI, percent body fat (obtained from bioelectrical impedance analysis), and waist circumference. For participants who provided additional genetic consent, a blood sample was taken for genetic testing that included *APOE* ε4 genotyping.

Statistical Analyses

Descriptive statistics were prepared to characterize the study population and to examine differences between sexes. Continuous variables were summarized using means and standard deviations, while frequency distributions were used for categorical variables. Chi square tests were used to identify

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Table 1. Baseline characteristics for participants ($n = 226$) in the *Brain in Motion* Study, Calgary, Alberta, Canada

	Male		Female			
Variable	*N*		*N*		T or χ^2 statistics	*p*-Value[a]
Demographics						
Age (years): *M*(*SD*)	108	67.0(6.9)	118	66.1(6.0)	0.98	.33
Retirement status (%)	108		118			
Yes	52	39.8%	74	62.7%	5.0	.084
Semi	13	12.0%	9	7.6%		
No	43	39.8%	35	29.7%		
Education (years): *M*(*SD*)	108	16.3(2.8)	118	15.7(2.2)	1.8	.08
NAART Estimated IQ: *M*(*SD*)	107	110(6.9)	116	111.2(6.0)	−1.4	.16
Health status						
$\dot{V}O_2$ max fitness (mL/kg/min): *M*(*SD*)	108	28.9(5.0)	118	23.6(4.4)	8.4	<.0001
Blood pressure (mm Hg)						
Systolic: *M*(*SD*)	108	126.24(14.44)	118	123.98(16.90)	1.1	.28
Diastolic: *M*(*SD*)	108	75.12(7.31)	118	70.04(9.08)	4.6	<.0001
Weight (kg): *M*(*SD*)	108	87.0(11.3)	118	70.2(11.9)	10.9	<.0001
BMI (kg/m^2): *M*(*SD*)	108	28.0(3.4)	118	26.6(4.1)	2.8	.005
Waist circumference (cm): *M*(*SD*)	105	101.7(9.7)	118	91.9(11.7)	6.8	<.0001
Genetic characteristics	104		113			
APOE ε4 − (%)	70	69.3%	87	78.4%	2.3	.13
APOE ε4 + (%)	31	30.7%	24	21.6%		
Lifestyle						
Alcohol consumption (g/day): *M*(*SD*)	87	13.4(16.4)	98	9.4(15.0)	1.7	.09
Calories consumed per day: *M*(*SD*)	87	1803(669)	98	1424(497)	4.4	<.001
Smoking status (% Ever smoked)	108	53.70%	118	39.83%	4.4	.04
Indices of cerebrovascular blood flow: M(SD)						
$\overline{V}$P	106	49.1(11.4)	116	56.9(12.4)	−4.9	<.0001
CVC	106	0.5(0.1)	116	0.7(0.2)	−6.0	<.0001
$\overline{V}$P reactivity	106	2.1(0.9)	116	2.3(1.0)	−1.3	0.20
CVC reactivity	106	0.01(0.007)	116	0.01(0.01)	−1.3	0.21

Note. T-statistics for continuous data and Chi^2 statistics for categorical data.
[a]All *p*-values are comparing differences between males and females.
NAART = North American Adult Reading Test; $\dot{V}O_2$ max = Maximal oxygen uptake; BMI = Body mass index; *APOE* ε4 = Apolipoprotein ε4 genotype; $\overline{V}$P = blood flow velocity at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; $\overline{V}$P reactivity = cerebral blood flow reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg; CVC reactivity = cerebrovascular conductance reactivity to a hypercapnic challenge from +1 mmHg to +8 mmHg.

between-group differences for categorical variables and a Spearman's correlation was used to assess potential collinearity among predictor variables. The global cognition and sub-domain *Z*-scores were calculated from raw data. Both cognitive and cerebrovascular outcome measures were assessed for normality using the Shapiro-Wilk test (Shapiro & Wilk, 1965). Continuous variables considered as confounders were age, NAART, mood, $\dot{V}O_2$ max, blood pressure, BMI, percent body fat, waist circumference, waist to hip ratio, cholesterol, HDL, LDL, total HDL, triglycerides, fasting glucose, alcohol consumption, and calories consumed/day. While the categorical variables considered were sex, marital status, income, retirement status, education, hypertensive status, hypercholesterolemia, smoking status, and *APOE* ε4 genotype. Multiple robust linear regression analyses were used with all final lifetime PA models using lifetime PA predictors adjusting for age, sex, NAART, $\dot{V}O_2$ max, BMI, and interaction terms (age-sex, age-predictor, sex-predictor, age-sex-predictor). Final covariates were chosen using both stepwise regression and assessment of the coefficient of determination (model R^2). All other variables were disregarded, since they did not improve the fit of the model. In subsequent analyses looking at the type, intensity and life period of PA, each respective grouping of activity was also controlled for (e.g., model for recreational PA adjusts for occupational and household activity). To characterize the relation between lifetime PA and cognitive functioning, while properly addressing the potential mediating effects of cerebrovascular indices (CVC, $\overline{V}$P, CVC reactivity and $\overline{V}$P reactivity), mediation analysis was used (Baron & Kenny, 1986). To test the hypothesis that cerebrovascular function mediates the lifetime PA-cognitive functioning relation, the results of robust linear regression were assessed to determine if statistical significance ($\alpha = 0.05$) was achieved. The following inter-relations required for mediation were assessed: the predictor lifetime PA had to be significantly associated with both the outcome cognitive functioning and the mediator cerebrovascular regulation, and cerebrovascular regulation had to be significantly associated with cognitive functioning. If these relations were statistically significant, the Sobel's test was used to determine the significance of the

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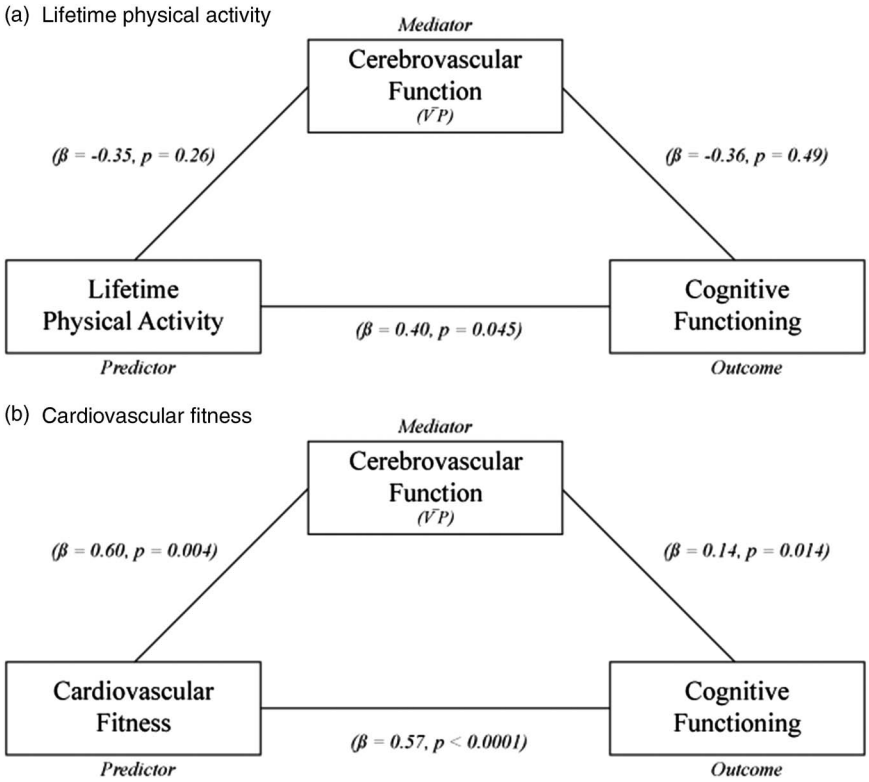

Fig. 2. Analytical framework for mediation analysis.
Note: $\overline{VP}$ was used as a representative measure of cerebrovascular function in this model.

indirect mediating effects, or the amount of mediation present (Baron & Kenny, 1986). Figure 2 represents the analytical framework for mediation analysis highlighting relevant regression coefficients.

Two *post hoc* mediation analyses were performed assessing the relation between past year PA and current fitness on cognitive performance, assessing the mediating effect of cerebrovascular function to determine if current PA levels or fitness are more important for cerebrovascular health and cognitive function than lifetime exposure. All predictors were evaluated for statistical significance at $\alpha = 0.05$. To assess the fit of each model, R^2 was used to measure the proportion of variance in the dependent variable that is explained by the robust linear model. To adjust for multiple regression comparisons, a Bonferroni correction was calculated for the analyses performed for type, intensity, and timing of PA if the main relation of interest was significant (Figure 3). No corrections were calculated for the between-group differences in Tables 1, 2, and 3, as these were for descriptive purposes. All statistical analyses were performed in STATA 13.1 (StataCorp, 2013).

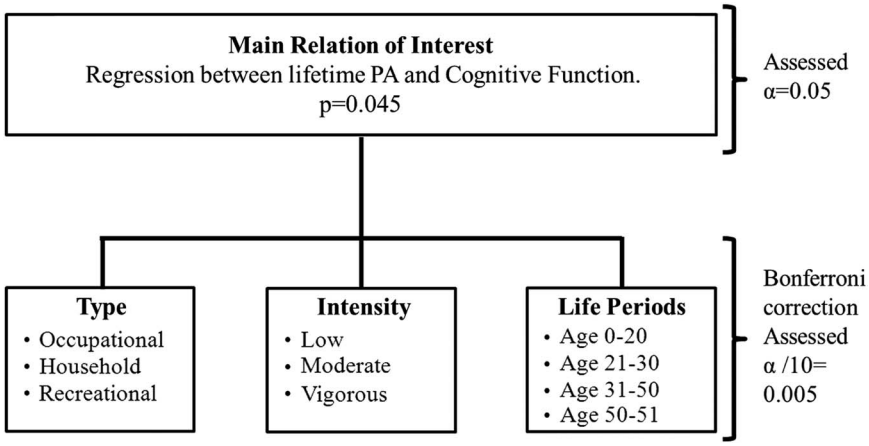

Fig. 3. Methodological structure for determining multiple regression adjustments. The main relationship had to be significant at 0.05 to proceed with any other analyses.

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Table 2. Average lifetime physical activity measures for male and female participants (n = 226) in the *Brain in Motion* Study, Calgary, Alberta, Canada

Variable	Male (n = 108) M (SD)	Female (n = 118) M (SD)	T-statistic	p-Value[a]
Lifetime total physical activity (MET-hr/wk/yr)	122.2(37.1)	127.3(39.2)	–1.0	.32
Past year physical activity (MET-hr/wk)	129.8(95.1)	131.8(88.3)	–0.16	0.87
Lifetime physical activity by type (MET-hr/wk/yr)				
Non-sedentary occupational physical activity	45.4(34.2)	30.9(26.7)	3.6	<.0001
Sedentary occupational physical activity	25.7(13.5)	16.1(10.7)	6.0	<.0001
Transportation physical activity	1.7(3.4)	1.1(1.7)	1.9	.06
Household physical activity	23.6(14.2)	58.5(33.1)	–10.1	<.0001
Recreational physical activity	25.8(13.4)	20.8(11.4)	3.1	.003
Lifetime physical activity intensity levels (hr/wk/yr)				
Low-intensity activity (<3 METs)	6.7(5.9)	12.0(8.3)	–5.3	<.0001
Moderate-intensity activity (3–6 METs)	17.1(10.5)	18.1(10.9)	–0.78	.46
Vigorous-intensity activity (≥6 METs)	1.8(1.9)	2.2(3.5)	–0.86	.30
Time periods of physical activity (MET-hr/wk/yr)				
0–20 years old	71.1(31.8)	65.6(31.8)	1.3	.19
21–35 years old	112.9(72.7)	139.2(63.3)	–2.9	.004
36–50 years old	112.8(71.1)	147.5(66.5)	–3.8	<.001
51–65 years old	103.4(56.2)	118.5(65.8)	–1.9	.066

[a]All p-values are comparing differences between males and females.
MET(s) = metabolic equivalents.

RESULTS

Demographics

Participants had a mean age of 66.5 ± 6.4 years (n = 226; 118 females) on study entry, were well educated with a moderate to high socioeconomic status, and 55.8% were retired (Table 1). Table 1 provides information on demographic, health, genetic, lifestyle, and cerebrovascular measures. The distributions of the *APOE* ε4 allele are similar to those found in the general population; 25.9% of participants were *APOE* ε4 + while 74.1% were *APOE* ε4- (McKay et al., 2011). Descriptive statistics for lifetime PA are presented in Table 2. As expected, the neuropsychological raw test scores had few absolute sex differences (Kimura & Hampson, 1994), but the female advantages on verbal tests are consistent with known sex effects on memory and verbal fluency (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; Kramer, Delis, & Daniel, 1988; Weiss, Kemmler, Deisenhammer, Fleischhacker, & Delazer, 2003). See Supplementary Table 1.

Table 3. Result of robust regression for the association between lifetime physical activity and global cognition, including all predictors that were adjusted for

	Global Cognitive Performance	
Predictor	Regression coefficients (*SE*)	p-Value
Lifetime total PA	0.40(0.20)	.045*
Age	0.038(0.40)	.92
Sex	62.26(37.26)	.096
NAART	0.62(0.078)	.000
$\dot{V}O_2$ max	0.077(0.14)	.59
BMI	0.21(0.15)	.18
Age-sex	–0.93(0.20)	.097
Age-lifetime PA	–0.0063(0.0031)	.045
Sex-lifetime PA	–0.55(0.29)	.056
Age-sex-lifetime PA interaction	0.0087(0.0044)	.047
Constant	–78.08(29.77)	.009

Note. Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$ max, BMI, age-sex, age-lifetime PA, sex-lifetime PA, and age-sex-lifetime PA.
R^2 attributable to lifetime PA = 18.4%, Adjusted model R^2 = 34.7%.
*$p < .05$ for the overall relationship between lifetime PA and global cognitive performance.
PA = physical activity; NAART = North American Adult Reading Test; $\dot{V}O_2$ max = maximal aerobic capacity; BMI = body mass index.

Lifetime PA and Current Cognitive Function

Cognitive and cerebrovascular outcomes were not normally distributed. Since no transformations resolved the issue with non-normal distributions, robust linear regression was used. Three participants had missing NAART scores since English was a second language and were excluded from all analyses. Results presented are for the remaining 223 participants (n = 116 female). All analyses using measures of lifetime PA controlled for age, sex, NAART, $\dot{V}O_2$ max, and interaction terms age-sex, age-lifetime PA, sex-lifetime PA, age-sex-lifetime PA. The adjusted model for the relation between lifetime PA and cognitive functioning is significant (p = .045). With every unit increase in MET-hr/week/year of

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Table 4. Adjusted models for the relation between type, intensity and life periods of physical activity and cognition

Predictor	Outcome variable	Regression coefficients (*SE*)	*p*-Value	Model R^2 %
Type (MET-hour/week/year)	Global Cognition			
Non-sedentary occupational physical activity		0.42(0.23)	0.074	34.7
Household physical activity		–0.51(0.50)	0.31	34.6
Recreational physical activity		1.18(0.49)	0.021*	35.0
Intensity (hour/week/year)	Global Cognition			
Low (0–3 METs)		–0.97(1.0)	0.33	34.6
Moderate (3–6 METs)		0.43(0.69)	0.53	34.0
Vigorous (>6 METs)		9.85(3.36)	0.004^{δ}*	36.0
Life periods (MET-hour/week/year)	Global Cognition			
Age 0 to 20		0.47(0.23)	0.036*	35.3
Age 21 to 35		0.36(0.099)	0.000^{δ}*	36.1
Age 36 to 50		0.059(0.10)	0.57	34.2
Age 51 to 65		–0.13(0.12)	0.28	34.7

Note. Multivariable adjusted for age at the time of LTPAQ interview, NAART, $\dot{V}O_2$ max, BMI and interaction terms (age–sex, age–lifetime PA predictor, sex–lifetime PA predictor, age–sex–lifetime PA predictor).
*$p < 0.05$.
$^{\delta}$*$p < 0.005$ (Bonferonni corrected *p*-value).
MET(s) = metabolic equivalent.

lifetime total PA, there was a 0.40 increase in global cognition *Z*-score (Table 3).

Figure 4 describes the significant three-way interaction between age, sex and lifetime PA, using age categories to depict the interaction. This statistically significant interaction indicates that the relation between lifetime PA and global cognition differs by sex and age; for males the amount of lifetime PA decreases with increasing age with the opposite relation observed in females. Figure 5 describes how cognitive performance changes with increasing lifetime PA using age categories (≤65 and >65) for males and females. There was a significant difference between global cognition scores between males and females at all lifetime PA levels ($p < .05$), and males have increasing cognition score as levels of lifetime PA increase ($p < .0001$) (Figure 5). Lifetime PA was not associated with any measures of cerebrovascular health, and cerebrovascular measures were not associated with cognition scores (data not shown).

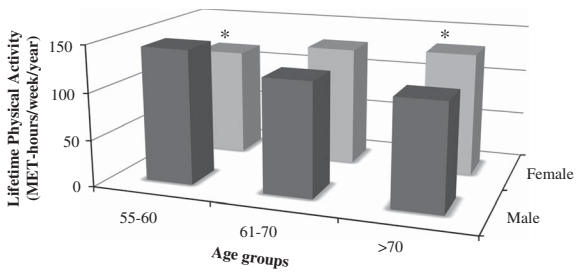

Fig. 4. Interaction between age, sex and lifetime physical activity. *p-value < .05.
Note: Age group trichotomized to display interaction, continuous variable used in all analyses.

Relative Components of Lifetime PA and Current Cognitive Function

The relation between lifetime PA and global cognition was significant at $\alpha = 0.05$; therefore, subsequent analyses were performed assessing type, intensity, and timing of PA (Figure 3). The results presented for the type, intensity, and timing of PA adjust for the same covariates and interaction terms as the main relation between total lifetime PA and cognition. There were statistically significant relations between lifetime recreational PA, vigorous intensity PA, and PA done between childhood to age 20 and age 21 to age 35. Specifically, for every unit increase in MET-hr/week/year of lifetime recreational PA there was a 1.18 increase in global cognition *Z*-score ($p = .021$). For vigorous intensity PA over lifetime, there was a 9.85 increase in global cognition *Z*-score for every hr/week of activity ($p = .004$). For every unit increase in MET-hr/week/year of PA from early childhood to age 20, there was a 0.47 increase ($p = .036$), and for activity between the ages of 21 and 35 years old, there was a 0.36 increase in global cognition *Z*-score ($p < .0001$). Table 4 summarizes the results for the associations between type, dose, and timing of lifetime PA and their associations with cerebrovascular indices, if significant. The three-way interaction between age, sex, and predictor was used in these analyses; however, the interaction effect is not shown. These analyses were repeated controlling for all other types of activity, all other intensities, and all other life periods in the same multivariate model (Table 5). These relations remained significant indicating the unique variance of these findings. Physical activity done from age 21 to 35 switched from significant to trending toward significance ($p = .053$) when controlling for all age periods; however, when just controlling for past year PA, it remained

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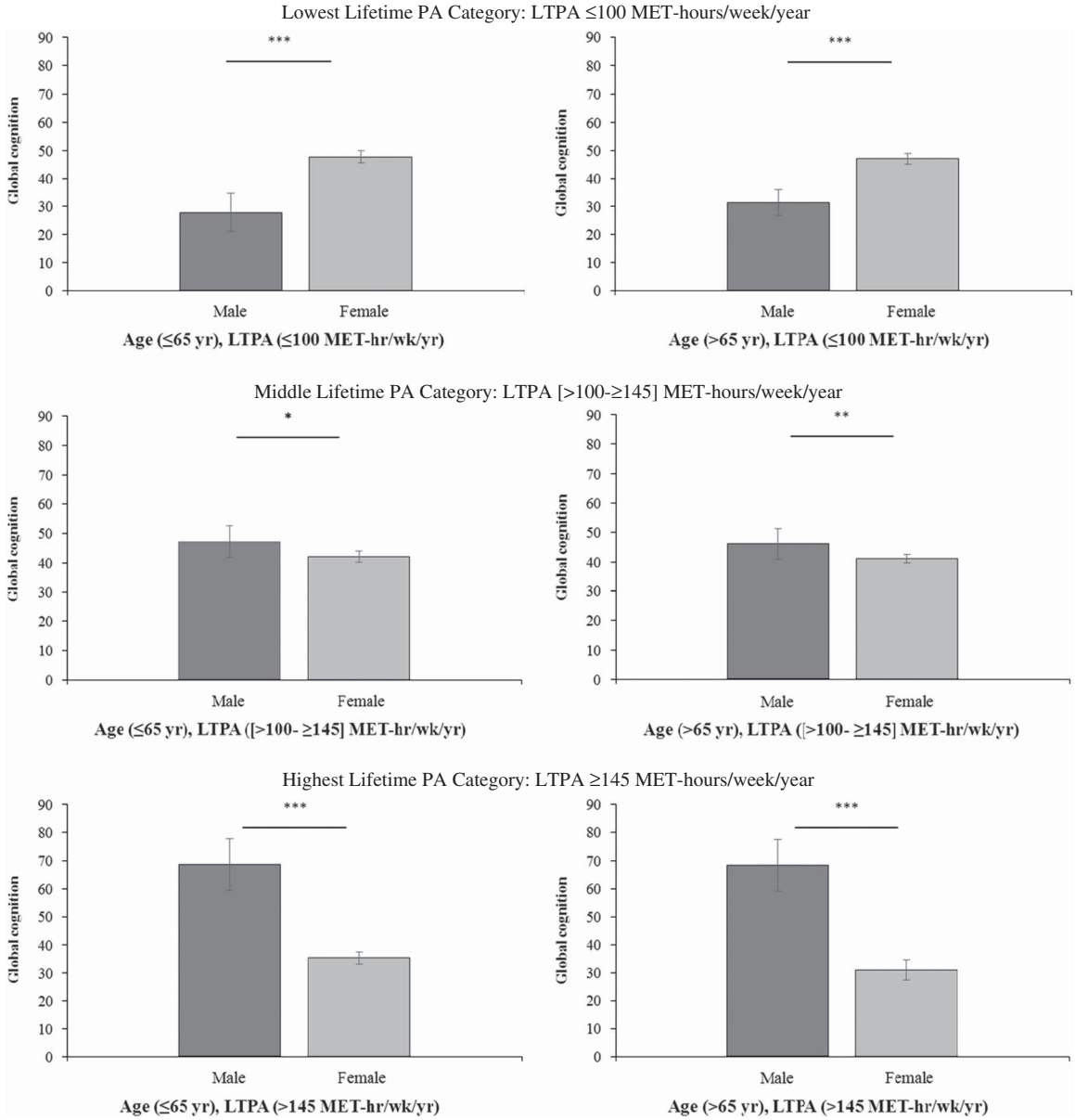

Fig. 5. Relation between lifetime PA and global cognitive performance. Created using regression coefficients from Table 3. ***p-value < .0001. **p-value < .001. *p-value < .005.

significant (Table 5). The second level of analyses (type, intensity, and timing) were assessed at both $\alpha = 0.05$ and $\alpha = 0.005$ based on a Bonferroni correction (Tables 4 and 5).

Current Measures and Current Cognitive Function

In addition to long-term effects of PA, we also examined relatively acute effects of fitness and past year PA. All *post hoc* analyses were adjusted for sex, NAART, waist circumference, blood pressure, smoking status, and alcohol consumption, and revealed a statistically significant relation between past year PA and global cognition ($p = .019$) (Table 6), with no mediating effects of cerebrovascular indices (data not shown). Past year PA was associated with current $\dot{V}O_2$ max ($p < .0001$). In contrast, relations were observed between current fitness ($\dot{V}O_2$ max), global cognition, and cerebrovascular health using mediation analysis (Figure 2b). For every one unit increase (ml/kg/min) in $\dot{V}O_2$ max, there was a 0.57 increase in global cognition Z-score ($p < .001$) (Table 6); for every one unit increase in $\dot{V}O_2$ max, there was a 0.60 unit increase in CVC ($p = .004$) and a 0.0081 unit increase in $\overline{V}P$ ($p = .001$) (Supplementary Table 2). Finally, with every one unit increase in CVC, there was a 13.31 increase in global cognition Z-score ($p = .005$) while for $\overline{V}P$ there was a 0.14 increase in global cognition Z-score ($p = .014$) (Supplemental Table 3). The first three pathways of mediation were statistically significant; therefore, the estimated indirect effect of CVC was calculated and accounted for approximately 13.3% of the total effect of $\dot{V}O_2$

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Table 5. Adjusted models for the relation between type, intensity, and life periods of physical activity and global cognition when also adjusting for respective types, intensities, or life periods

Predictor	Regression coefficients (*SE*)	*p*-Value	Model R^2 %
Type (MET-hour/week/year)[a]			
Non-sedentary Occupational physical activity	0.42(0.23)*	.072	35.2
Household physical activity	–0.50(0.50)	.32	34.6
Recreational physical activity	1.19(0.51)	.019*	35.6
Intensity (Hour/week/year)[a]			
Low (0–3 METs)	-0.85(0.99)	.39	35.3
Moderate (3–6 METs)	0.33(0.69)	.64	34.7
Vigorous (>6 METs)	8.93(3.47)	.011*	35.9
Life Periods (MET-hour/week/year)[a]			
Age 0 to 20	0.46(0.23)	.053	35.1
Age 21 to 35	0.33(0.10)	.001$^{\delta}$*	36.6
Age 36 to 50	0.056(0.11)	.60	34.4
Age 51 to 65	–0.11(0.13)	.39	35.3
Life Periods (MET-hour/week/year)[b]			
Age 0 to 20	0.48(0.23)	.038*	35.2
Age 21 to 35	0.36(0.10)	.000$^{\delta}$*	36.1
Age 36 to 50	0.052(0.11)	.63	34.2
Age 51 to 65	–0.16(0.13)	.21	35.0

[a]Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$ max, BMI, respective physical activity groupings, and interaction terms (age-sex, age-predictor, sex-predictor, age-sex-predictor).
[b]Multivariable adjusted for age at the time of LTPAQ interview, sex, NAART, $\dot{V}O_2$ max, BMI, past year PA, and interaction terms (age-sex, age-predictor, sex-predictor, age-sex-predictor).
*$p < 0.05$.
$^{\delta}$*$p < 0.005$ (Bonferonni corrected *p*-value).
MET(s) = metabolic equivalents.

Table 6. Adjusted overall model for associations between past year physical activity and global cognition and current fitness ($\dot{V}O_2$ max) and global cognition

	Global Cognitive Performance	
Predictor	Regression coefficients (*SE*)	*p*-Value
Past year PA	0.018(0.008)	.019
Sex	3.50(1.45)	.016
NAART	0.60(0.10)	.000
Waist circumference	0.030(0.060)	.62
Blood pressure	0.10(0.081)	.20
Smoking status	1.74(1.29)	.18
Alcohol consumption	0.024(0.57)	.97
Constant	–81.07(13.27)	.000
$\dot{V}O_2$ max	0.57(0.15)	.000
Sex	7.80(1.77)	.000
NAART	0.58(0.098)	.000
Waist circumference	0.14(0.068)	.042
Blood pressure	0.082(0.080)	.30
Smoking status	1.74(1.26)	.16
Alcohol consumption	–0.038(0.56)	.95
Constant	–102.42(14.61)	.000

Note. Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status. and alcohol consumption. R^2 attributable to Past year PA = 0.15%, Adjusted model R^2 = 21.4%. R^2 attributable to $\dot{V}O_2$ max = 0.44%, Adjusted model R^2 = 23.6%.
PA = physical activity; NAART = North American Adult Reading Test; $\dot{V}O_2$ max = maximal aerobic capacity.

max on cognition, while $\overline{V}$P accounted for 8.4%. However, the Sobel test revealed that the indirect effect of CVC and $\overline{V}$P on the relation between $\dot{V}O_2$ max, and cognition was not statistically significant ($p = .089$ and $p = .17$, respectively).

DISCUSSION

The primary finding for this study demonstrated that greater total lifetime PA is associated with better global cognitive performance. The impact of lifetime PA on global cognitive performance differed for males and females as a result of an interaction between age, sex, and lifetime PA. In our sample, males followed the expected trajectory of increased global cognitive performance with increased levels of lifetime PA, whereas females did not (Figure 5). Many studies have reported no difference between males and females when assessing the relation between PA and cognition (Chang et al., 2010; Middleton, Mitnitski, Fallah, Kirkland, & Rockwood, 2008; Wendell et al., 2014). Furthermore, evidence from all-male studies suggests a positive associations between increasing PA levels and decreased risk of cognitive impairment, Alzheimer's disease, and related dementias (Abbott et al., 2004; van Gelder et al., 2004). Our findings are contrary to the hypothesis that the effects of PA on cognitive functioning may be more prominent in women (Brown et al., 2013; Colcombe & Kramer, 2003; Ho et al., 2001; Laurin et al., 2001). It has been proposed that women should show greater cognitive change in response to exercise as compared to men, due to the variation in cognitive strengths between men and women. This differential sensitivity may be a result of organizational effects of sex hormones (Kimura, 2002; Kimura & Hampson, 1994; Kramer & Erickson, 2007). Declines in circulating sex steroid hormones associated with aging have been implicated as underlying age-related changes in brain health that differ for males and females. Specifically, there is evidence of altered CBF (Matteis et al., 1998), volume of the frontal and temporal lobes of the brain (Cowell et al., 1994), and increases in an indicator of cortical atrophy, increased ventricular and peripheral cerebrospinal fluid volume (Coffey et al., 1998) in older men, compared to women.

Our finding that increased PA during lifetime is associated with greater cognitive functioning in middle-aged and older adults accords with findings from a recent systematic review and meta-analysis by Blondell et al. (2014). Previous literature indicates that increasing levels of PA in later life improved cognitive performance, decreased the risk for cognitive decline after the age of 55 years (Brown et al., 2013; Buchman et al., 2012; Laurin et al., 2001; Middleton et al., 2008; van Gelder et al., 2004), and decreased the risk of developing dementia and Alzheimer's disease (Abbott et al., 2004;

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Buchman et al., 2012; de Bruijn et al., 2013; Laurin et al., 2001; Scarmeas et al., 2009). To date, no study has sought to combine information on the duration, frequency, and intensity of all types of activity to create one comprehensive measure describing the average volume of PA completed across the lifetime. Therefore, using the measure of average MET-hr/week/year of PA provides novel insight into the positive effects that higher levels of PA throughout life will have on cognitive abilities in older age.

Timing and intensity of activity were also deemed to be important in the relation between PA and cognitive performance. When assessing the association between lifetime engagement in low, moderate, or vigorous PA and cognitive functioning, only vigorous intensity activity was associated with better global cognitive performance. The average hr/week/year of vigorous intensity PA over lifetime had the greatest impact on global cognition *Z*-scores, indicating vigorous intensity activity may be the most important for maintaining cognitive functioning into old age. Our findings align with the results of the Finnish Twin Cohort study (Iso-Markku, Waller, Kujala, & Kaprio, 2015) showing that participants who persistently engaged in vigorous activity in midlife had a decreased risk of mortality from dementia (Iso-Markku et al., 2015). Our findings also provide evidence that vigorous intensity activity above low or moderate intensity will help reduce cognitive deficit and potentially other devastating effects of dementia. Furthermore, lifetime recreational (including transportation) activity was independently associated with greater cognitive functioning. This finding aligns with previous investigations suggesting that current engagement in leisure time or recreational activities is associated with better cognitive function into older age (Rovio et al., 2005; Weuve et al., 2004; Yaffe et al., 2001). This finding promotes the etiologic role of sustained, planned PA throughout life for delaying or preventing age-related cognitive decline.

Physical activity in early childhood to midlife (age 0–35 years) had a substantial impact on better global cognitive performance at an older age. Several studies have assessed PA in midlife (i.e., 40–60 years) and have reported an association between greater midlife activity and a reduced incidence of dementia (Andel et al., 2008; Chang et al., 2010; Kareholt et al., 2011; Rovio et al., 2005; Sun et al., 2010; Tolppanen et al., 2015). These results are contradictory with our findings of PA in early life being associated with improved cognitive performance in middle and older age. Relations may not have been observed in midlife as a result of our sample being sedentary before enrollment (age 50–65 years or midlife for many participants). It is likely that many individuals in our sample have been more sedentary in years leading up to the assessment than in early life. However, our findings closely align with Middleton (2010) who assessed self-reported PA at multiple points in time, and found that the strongest relationship was between the level of PA during adolescence and cognitive status during later life. Therefore, more research is warranted to determine the life periods in which PA levels contribute to better cognitive abilities.

Although lifetime PA contributes to better cognitive performance in middle and older age, no associations were observed with measures of cerebrovascular function. Based on previous research, we hypothesized that measures of acute fitness or high levels of current PA may have more impact on cerebrovascular health. *Post hoc* analyses were performed assessing past year PA and current fitness, revealing $\dot{V}O_2$ max measured at baseline (i.e., in later life) was more predictive of cerebrovascular health than lifetime or past-year measures of PA. Similarly, Bailey et al. (2013) reported that adults who were more active doing recreational activities over lifetime (confirmed with $\dot{V}O_2$ max) had better cerebrovascular function. Previous literature has linked current fitness levels to enhanced cerebrovascular function (Ainslie et al., 2008; Barnes et al., 2013; Burdette et al., 2010) and improved cognition (Colcombe et al., 2004; Forbes et al., 2013; Kramer et al., 1999; Prakash et al., 2015, 2011). Therefore, by determining that measures of cerebrovascular health ($\overline{V}$P and CVC) partially mediate the relation between $\dot{V}O_2$ max and global cognitive performance provides evidence that cerebrovascular health may play a part in the relation between current fitness and cognition.

A major strength of this study was the comprehensive, reliable measure of lifetime total PA (Friedenreich et al., 1998), which captured types, intensities, and time periods in life when PA could be most beneficial for reducing cognitive decline associated with aging. Additionally, we were not limited in our analyses to fully explore the association between PA, cerebrovascular measures, and cognition. An additional strength was the unique testing protocols, such as the extensive neuropsychological test battery for cognitive abilities and the CBF test for cerebrovascular measurements (Brown et al., 2010; Tyndall et al., 2013). Finally, the quality and extent of participant information collected permitted a full assessment of covariates in the analysis.

Lifetime PA and other factors (i.e., age, sex, NAART, $\dot{V}O_2$ max, BMI, age-sex, age-lifetime PA, sex-lifetime PA, and age-sex-lifetime PA interactions) explain between 34.0% and 36.1% of the variance in global cognition. A better model fit could be potentially obtained by considering factors such as current social activities, history of depression, or family history. Additionally, it is possible that other factors may have mediated the relation between lifetime PA and cognitive functioning. In the future when assessing lifetime measures of PA, it would be beneficial to explore biological and environmental factors as mediators that may have an impact over one's lifetime such as history of socio-economic status (impacting opportunities over one's lifetime) or intellectual ability in the individual's youth (impacting decisions to participate in PA).

We did not collect information on hormone levels at baseline; therefore, we are limited in our ability to fully explore the reason for observed sex differences between males and females. Further our findings have limited generalizability to all older adults given that it is based on a highly educated, mostly Caucasian volunteer sample. There is the possibility of misclassification of lifetime PA since participants may not have been able to recall their activities

accurately. However, given that questionnaire has high reproducibility (Friedenreich et al., 1998), we anticipate the effect of this measurement error to be minimal and any misclassification to be non-differential with the effect of reducing our ability to show a relation between PA and cognition suggesting that these results are conservative estimates of the true effect. Additionally, the questionnaire has not been tested for validity. An ideal but unrealistic validation study would require historical PA data on a cohort of study participants assessed repeatedly over their lifetimes to capture the same data as are assessed in the LTPAQ used here. It is possible that PA from earlier in life is not accurately captured.

We used the Bonferroni correction for multiple regression comparisons to reduce the risk of type I error. Using this correction resulted in loss of significance for some findings. Although we reduced type I error with a conservative α level, these corrections reduce statistical power and increase the risk of type II error; therefore, the corrected α level should be interpreted with caution (Rothman, 1990). Finally, a cross-sectional study design cannot assess causality. Recent research by Belsky et al. (2015) demonstrated that children with higher levels of cognitive ability choose healthier lifestyles, and also had improved cognitive functioning later in life. These findings suggest that causality cannot be concluded. However, there has also been evidence suggesting cognitive abilities are not consistent over one's lifespan and speculate that both innate abilities and lifestyle must be considered together rather than looking at them as separate entities for determining cognitive changes with aging (Deary, Whiteman, Starr, Whalley, & Fox, 2004). A prospective longitudinal study with multiple data collection and testing periods would be required to address this question more fully.

This study adds to previous evidence that PA protects against poor cognitive functioning in older age while providing new insight into the importance of lifetime PA and the potential mediating effects of cerebrovascular health. We found that total lifetime PA, specifically participation in recreational activities, hours spent in vigorous intensity activity over lifetime, and PA done in early childhood to midlife, are associated with improved global cognitive performance in older age. Although cerebrovascular health did not mediated the association between lifetime or past year PA and global cognition, it appeared to partially mediate the association between current fitness levels and global cognition in middle-aged and older adults. Thus, higher levels of PA throughout life and in the past year of life are associated with better cognitive functioning in older age, while current fitness levels may be more important for improved cerebrovascular health in addition to cognitive functioning. This difference emphasizes the finding that cerebrovascular health may be more closely linked to physiological measures of fitness than subjective measures of activity.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1355617715000880

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