**SUPPLEMENTAL MATERIALS**

**Supplemental Cerebrovascular Blood Flow Testing Methods**

Participants underwent a two-hour assessment administered by trained staff. Two hours prior to testing, participants fasted and refrained from exercising. Blood flow velocity of the middle cerebral artery (MCAv) was measured non-invasively using a 2-MHz pulsed transcranial Doppler ultrasound system (TCD; Toc Neurovision™, Multigon Industries, Inc., Yonkers, NY) (Aaslid et al., 1982; Poulin et al., 1996; Poulin & Robbins, 1996). Peak MCAv, heart rate, beat-by-beat blood pressure measurements using finger pulse photoplethysmography; corroborated with three resting brachial measurements, and arterial O2 saturation (finger pulse oximetry) were measured continuously throughout the protocol, as previously described (Brown et al., 2010). Dedicated software (Chamber, University Laboratory of Physiology, Oxford, UK) recorded end-tidal PCO2 and PO2 (PETCO2 and PETO2) during 10 minutes of seated rest. Each participant had their nose occluded 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 (AMIS 2000, Innovision, Odense, Denmark) measured the concentration of CO2 and O2 continuously at the mouth, and breath-by-breath values for end tidal CO2 (PETCO2) and O2 (PETO2) were determined. These end-tidal responses (PETCO2 and PETO2) were averaged over 10 minutes of seated rest and were used to determine the desired PETCO2 and PETO2 to assess the cerebrovascular response to the euoxic hypercapnia testing. Accurate control of desired PETCO2 and PETO2 values were continuously achieved using customized software (BreatheM v2.40, University Laboratory of Physiology, Oxford, UK), using the dynamic end-tidal forcing techniques (Poulin et al., 1996; Poulin, Liang, & Robbins, 1998), and experimental protocols (Brown et al., 2010, Tyndall et al., 2013), as previously described. The euoxic hypercapnia test lasted 12 minutes and included two 3-minute step increases in PETCO2 as previously described (Brown et al., 2010; Tyndall et al., 2013). Physiological responses were calculated as the mean response over the final 30 seconds of each stage during the hypercapnic challenge.

This protocol produced four measures of cerebrovascular function for analysis including peak velocity of blood moving through the MCA (), cerebrovascular conductance (CVC; MCAv/Mean Arterial Pressure) and and CVC reactivity during the hypercapnic challenge. Specifically reactivity was calculated as the change in divided by the change in PETCO2 from +1 to +8 mmHg while CVC reactivity is the change in CVC divided by the change in PETCO2 from +1 to +8 mmHg. These measures are widely used in the cerebrovascular literature employing transcranial Doppler ultrasound techniques (Aengevaeren et al., 2013; Ainslie et al., 2008; Bailey et al., 2013; Barnes et al., 2013; Brown et al., 2010; Demirkaya et al., 2008; Murrell et al., 2013; Zhu et al., 2013)

**Supplemental Table 1.** Raw test scores for cognitive sub-domains for male and female participants (n=226) in the *Brain in Motion* Study, Calgary, Alberta.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cognitive Test**  | **Males (n=108)****M (SD)** | **Females (n=118)****M (SD)** | **T-statistic** | **p-value**¥ |
| ***Verbal Memory*** |  |
| Buschke Selective Reminding Test Delayed Recall  | 7.23(2.41) | 8.64(2.06) | -4.8 | <.0001 |
| Buschke Selective Reminding Test Immediate Recall  | 44.68(7.62) | 50.41(6.83) | -6.0 | <.0001 |
| ***Figural Memory*** |  |
| Medical College of Georgia Complex Figures Test Delayed  | 27.61(6.06) | 27.13(5.96) | 0.60 | .55 |
| Medical College of Georgia Complex Figures Test Immediate | 28.31(6.09) | 27.75(5.47) | 0.74 | .46 |
| ***Processing Speed*** |  |
| D-KEFS Color Word Interference Color time | 40.44(93.14) | 38.34(89.17) | 1.7 | .09 |
| D-KEFS Color Word Interference Word time | 31.59(93.88) | 22.57(3.94) | -0.011 | .99 |
| Symbol-Digit Modalities Test Oral score | 62.57(91.40) | 56.57(8.45) | -2.1 | .04 |
| Symbol-Digit Modalities Test Written score | 47.48(9.25) | 49.42(7.02) | -1.8 | .08 |
| ***Executive Function*** |  |
| D-KEFS Color Word Interference Switch time | 73.77(91.40) | 64.86(17.18) | 0.12 | .91 |
| D-KEFS Color Word Interference Inhibit time | 71.47(91.50) | 60.49(11.71) | 1.2 | .23 |
| D-KEFS Verbal Fluency Category Switching  | 13.78(2.39) | 14.94(2.67) | -3.4 | <.001 |
| D-KEFS Verbal Fluency Test Target Words Correctly Produced | 41.34(10.55) | 43.27(11.80) | -1.3 | .20 |
| D-KEFS Card Sorting Recognition Description score | 18.35(6.08) | 18.87(6.04) | -0.65 | .52 |
| D-KEFS Card sorting Free Sort Description score | 18.35(6.08) | 18.87(6.04) | -0.65 | .52 |
| D-KEFS Card Sorting Free Sort: Number of Correct Sorts | 5.10(1.37) | 5.01(1.51) | 0.49 | .63 |
| ***Complex Attention*** |  |
| ACT Perseverations | 6.57(4.39) | 6.14(3.94) | 0.79 | .43 |
| ACT Total Correct  | 47.88(6.72) | 48.25(5.91) | -0.45 | .66 |
| ***Verbal Knowledge*** |  |
| D-KEFS Verbal Fluency Test: Category Fluency Score | 38.65(7.57) | 43.36(6.99) | -4.9 | <.0001 |
| ***Spatial Reasoning*** |  |
| Medical College of Georgia Complex Figures Test: Copy  | 35.47(1.11) | 35.56(0.86) | -0.66 | .51 |
| ***Global Cognition z-score***  | -1.48(10.72) | 2.20(8.45) | -2.87 | .004 |

*Abbreviations:* D-KEFS = Delis-Kaplan Executive Function System; ACT= Auditory Consonant Trigrams

¥P-values are comparing differences between males and females.

**Supplemental Table 2.** Adjusted models assessing the relations between max and cerebrovascular health indices.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome Variable**  | **Predictor** | **Regression Coefficients (SE)** | **p-value** | **Model R2 %** |
|  | max  | 0.60(0.21) | 0.004 | 14.9 |
|  | Sex | 9.96(2.41) | 0.000 |  |
|  | NAART | -0.032(0.13) | 0.81 |  |
|  | Waist Circumference  | -0.043(0.091) | 0.64 |  |
|  | Blood Pressure | -0.14(0.11) | 0.20 |  |
|  | Smoking Status  | 1.73(1.70) | 0.31 |  |
|  | Alcohol Consumption | 0.32(0.75) | 0.69 |  |
|  | Constant  | 48.19(19.68) | 0.015 |  |
| CVC | max  | 0.0080(0.0024) | 0.001 | 31.6 |
| Sex | 0.13(0.027) | 0.000 |  |
|  | NAART | 0.000029(0.0015) | 0.99 |  |
|  | Waist Circumference  | 0.00040(0.0010) | 0.70 |  |
|  | Blood Pressure | -0.0087(0.0012) | 0.000 |  |
|  | Smoking Status  | -0.0098(0.0031) | 0.20 |  |
|  | Alcohol Consumption | 0.00071(0.0086) | 0.93 |  |
|  | Constant  | 0.89(0.22) | 0.000 |  |
| reactivity  | max  | 0.021(0.017) | 0.21 | 5.1 |
| Sex | 0.33(0.19) | 0.092 |  |
|  | NAART | -0.16(0.011) | 0.14 |  |
|  | Waist Circumference  | 0.00020(0.0073) | 0.98 |  |
|  | Blood Pressure | -0.0066(0.0087) | 0.45 |  |
|  | Smoking Status  | -0.078(0.14) | 0.57 |  |
|  | Alcohol Consumption | 0.0014(0.060) | 0.98 |  |
|  | Constant  | 3.64(1.58) | 0.022 |  |
| CVC reactivity  | max  | 0.00020(0.00015) | 0.16 | 4.8 |
| Sex | 0.0016(0.0017) | 0.35 |  |
|  | NAART | -0.00014(0.000093) | 0.12 |  |
|  | Waist Circumference  | 0.0000055(0.000064) | 0.93 |  |
|  | Blood Pressure | -0.00011(0.000076) | 0.16 |  |
|  | Smoking Status  | -0.00052(0.0012) | 0.66 |  |
|  | Alcohol Consumption | -0.00067(0.00053) | 0.20 |  |
|  | Constant  | 0.030(0.013) | 0.029 |  |

*Abbreviation*: = cerebral blood flow at +1 mmHg; CVC = cerebrovascular conductance at +1 mmHg; 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, max = maximal aerobic capacity, NAART= North American Adult Reading Test.

Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.

**Supplement Table 3.** Adjusted overall models for associations between and CVC and the outcome of global cognition.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Global Cognition**  |  |  |
| **Exposure** | **Regression Coefficients (SE)** | **p-value** | **Model R2 %** |
|  | 0.14(0.055) | 0.014 | 21.3 |
| Sex | 2.27(1.51) | 0.14 |  |
| NAART | 0.60(0.10) | 0.000 |  |
| Waist Circumference  | 0.021(0.060) | 0.73 |  |
| Blood Pressure | 0.095(0.082) | 0.25 |  |
| Smoking Status  | 0.92(1.28) | 0.48 |  |
| Alcohol Consumption | 0.033(0.57) | 0.95 |  |
| Constant  | -82.03 | 0.000 |  |
|  |  |  |  |
| **CVC**  | 13.31(4.63) | 0.005 | 22.3 |
| Sex | 2.08(1.48) | 0.16 |  |
| NAART | 0.60(0.099) | 0.000 |  |
| Waist Circumference  | 0.030(0.059) | 0.61 |  |
| Blood Pressure | 0.19(0.087) | 0.032 |  |
| Smoking Status  | 0.89(1.27) | 0.49 |  |
| Alcohol Consumption | 0.023(0.56) | 0.97 |  |
| Constant  | -91.37 | 0.000 |  |
|  |  |  |  |

*Abbreviation:* CVC = cerebrovascular conductance at +1 mmHg; = cerebral blood flow at +1 mmHg; NAART= North American Adult Reading Test; BMI= body mass index.

Multivariable adjusted for sex, NAART, waist circumference, blood pressure, smoking status and alcohol consumption.