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Cardiovascular disease risk is associated with middle cerebral artery blood flow velocity in older adults

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Abstract

Purpose: The aim of this study was to evaluate the **relationship** of cardiovascular disease (CVD) on middle cerebral blood flow velocity (MCAv) at rest and during exercise. A secondary aim was to explore the relationship between MCAv and 1) the presence of white matter lesions and 2) cognitive function.

Methods: We recruited individuals who were cognitively normal older adults. CVD risk was assessed by the Pooled Cohort atherosclerotic cardiovascular disease (ASCVD) risk score. Transcranial Doppler ultrasound measured middle cerebral artery at rest and during a bout of moderate intensity exercise. We quantified white matter lesions from MRI and cognitive function outcomes included executive function, language, processing speed, and attention.

Results: Seventy-two participants 70.1 ± 4.7 years of age completed the study protocol. ASCVD risk score was significantly associated with resting and exercise MCAv ($p<0.01$) but not associated with white matter lesions ($p>0.468$). We observed a significant association between resting and exercise MCAv and language processing ($p=0.010$) but not other cognitive domains.

Conclusion: In cognitively normal older adults, higher ASCVD risk score was associated with blunted resting and exercise MCAv and with lower language processing performance. These results highlight the need for CVD risk management to maintain optimal brain health.

Keywords

ultrasound imaging; brain health; aging

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Introduction and Purpose

Cardiovascular disease (CVD) risk factors play a major role in late-life cognitive function, as well as the occurrence of stroke, vascular dementia, and Alzheimer's disease.[1,2] Impaired cerebrovascular regulation may be the foundational link between CVD risk and poor brain health.[3,45–8] Further, higher CVD risk in 142 middle aged and older adults was a significant predictor for lower brain blood flow velocity in both the carotid and middle cerebral arteries (MCA).[4] CVD risk and aortic stiffness can negatively affect cerebral blood flow in healthy, cognitively normal adults.[9] However, over time, impaired cerebral blood flow regulation may lead to repeated ischemic injury, such as white matter lesions (WML),[10] stroke, and even Alzheimer's disease.[11] Therefore, healthcare professionals on the front lines of care should assess CVD risk to maximize optimal brain health.

Understanding MCAv at rest and during an acute exercise challenge may provide valuable information for individuals at risk for cerebral pathology or suboptimal brain aging. Our prior work was the first to show a blunted cerebrovascular response during exercise in individuals with elevated beta-amyloid, a known risk factor for Alzheimer's disease[12] when compared to those who were non-elevated. With further examination between groups, we reported that participants with elevated beta-amyloid also had greater CVD risk. The already present elevated beta-amyloid potentially obscured our ability to identify the unique contributions of CVD risk to brain health. Therefore, to better understand **the relationship between** CVD risk on MCAv, we designed the present study to focus on individuals characterized as non-elevated for the presence of beta-amyloid and without cognitive impairment. The current study evaluated the **association** of CVD risk (defined as the atherosclerotic cardiovascular disease (ASCVD) risk score)[13] on MCAv at rest and during a single bout of moderate intensity exercise.

We hypothesized that individuals with higher ASCVD risk would have blunted MCAv at rest and during exercise. A second study objective was to explore the relationship between MCAv and 1) WML and 2) cognitive function. We hypothesized that blunted MCAv at rest and during exercise would be associated with higher WML and reduced cognitive function.

Methods

Participants

Participants were recruited from a registry of individuals at the University of XXX Alzheimer's Disease Center. Inclusion criteria were: 1) 65–90 years of age; 2) cognitively normal/non-demented based on neuropsychological testing and a Clinical Dementia Rating = 0; and 3) completion of [18F] Florbetapir positron emission tomography (PET) scan within 6 months of our experimental procedures. Exclusion criteria included: 1) Diagnostic and Statistical Manual of Mental Disorders-IV defined drug or alcohol abuse within the previous 2 years; 2) clinically significant depression or anxiety; 3) insulin-dependent diabetes; 4) myocardial infarction or symptoms of coronary artery disease within the previous 2 years; 5) acute decompensated congestive heart failure or class IV heart failure; 6) major orthopedic disability; 7) inability to exercise due to pain or physician restrictions.

For this study, we excluded individuals who were characterized as having elevated beta-amyloid status as previously reported.[12]

Written informed consent was obtained for all participants prior to any data collection. Approval for this study was granted by the Institutional Review Board at the University of XXX Medical Center.

Experimental procedure

All participants began study procedures between 7:30 and 9:00am. Participants abstained from caffeine for 12 hours, physical activity for 24 hours and a large meal for 2 hours.[12,14] Participants were asked to refrain from taking their morning medications until after the procedure. After consent, health questionnaires including assessment of CVD risk factors were completed followed by the experimental protocol to assess cerebrovascular regulation.

Cardiovascular disease risk

We calculated ASCVD risk using the Pooled Cohort Equation provided by the American Heart Association and the American College of Cardiology *Guideline on the Assessment of Cardiovascular Risk*.[13] The ASCVD risk score was calculated using the Pooled Cohort equation which incorporates gender, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (SBP), as well as smoking, diabetes and hypertension treatment status.[13] Supine SBP was assessed after 20 minutes of rest. Cholesterol values were obtained during the clinic visit to the XX Alzheimer's Disease Center between 1–2 months prior to the TCD measures.

Middle Cerebral Artery Blood Flow Velocity

The laboratory room for the experimental session was dimly lit, the temperature was maintained between 22–24 degrees Celsius and external stimuli were kept to a minimum during testing.[15–17] Unpublished data from an existing dataset (n = 70) in our laboratory demonstrated that the mean intra-trial coefficient of variation during the resting condition was 7.7% for MCA velocity ($MCAv_{mean}$), 6.7% for mean arterial pressure (MAP) and 8.6% for end-tidal carbon dioxide ($P_{ET}CO_2$) and during the exercise condition $MCAv_{mean}$ was 10.0%, 7.9% for MAP and 8.0% for $P_{ET}CO_2$.

All participants sat quietly on the exercise device for 15 minutes during the experimental protocol set up. The study team member (YL, SP) performing the transcranial Doppler (TCD) ultrasound scan was blinded to any information related to medical history, cardiovascular risk status and any imaging data related to amyloid or white matter lesions. The MCA was measured using transcranial Doppler (TCD) ultrasound. The headset with a 2-MHz robotic probe (RobotoC2MD, Multigon Industries) was placed on the temporal window and fixed in place. The left MCA was the primary vessel of interest. If a signal was not obtainable, then the right MCA was used.[12,15] Once the optimal signal was identified, the imaging process began for mean MCAv ($MCAv_{mean}$) at rest and during exercise. MAP was measured using a finger plethysmograph (Finometer Pro, Finapres Medical Systems), which was placed on the middle finger of the left hand. A nasal cannula was placed in the participants' nares and adjusted as needed to ensure optimal $P_{ET}CO_2$ reading. (BCI

Capnocheck 9004) We monitored $P_{ET}CO_2$ during exercise to ensure participants were not hyperventilating, which is known to induce cerebral vasoconstriction and lower cerebral blood flow.[18] Heart rate (HR) was measured using a 5-lead electrocardiogram. MAP, $P_{ET}CO_2$ and $MCAv_{mean}$ were averaged across each condition (rest and exercise).

For the seated rest condition, participants sat quietly on a recumbent stepper (NuStep, T5XR). Baseline data for all variables was recorded for 8 minutes. After the rest condition, participants performed a single bout of exercise at moderate intensity using the recumbent stepper. Moderate intensity was defined as 40% - 60% of age-predicted heart rate (HR) reserve.[19] Participants were instructed to maintain a step rate of approximately 90 steps per minute.[20] All participants began the exercise at 40 watts. The resistance was then increased until the target HR range was reached. Once participants were in steady state for one continuous minute, the 8-minute exercise session began. Data were sampled at 500 Hz using an analog to digital data acquisition board (National Instruments) and custom script written for MATLAB (v2015, Mathworks).

White matter lesions

The NeuroImaging Core of the XX Alzheimer's Disease Center performed data acquisition for the MRI according to the Alzheimer's Disease Neuroimaging Initiative, which a multisite longitudinal study of aging and dementia. Our neuroimaging facility uses a Siemens 3.0 Tesla scanner high-resolution T1 weighted and T2 for anatomical assessment (MP-RAGE; 1*1*1.2mm voxels; TR = 2300ms, TE = 2.98ms, TI = 900ms, FOV 256mm, 9 degree flip angle). Lesions were segmented by the lesion growth algorithm[21] as recommended and implemented in the LST toolbox version 2.0.15 (www.statisticalmodelling.de/lst.html) for SPM12. The algorithm first segments the MP-RAGE T1 images into the three main tissue classes (cerebrospinal fluid, gray matter, white matter). This information is then combined with the co-registered FLAIR (0.9*0.9*5mm voxels; TR: 9000ms, TE=91ms, TI=2500ms, FOV 240mm, 150-degree flip angle) intensities in order to calculate lesion belief maps. By thresholding these maps with a pre-chosen initial threshold (k=.13) an initial binary lesion map is obtained and subsequently grown according to hyperintensities in the FLAIR image to produce a lesion probability map. The optimal initial lesion threshold was identified as the consensus of 3 raters visually inspecting lesion probability maps in two independent data sets (n=5 age-matched older adults, n=5 individuals with multiple sclerosis). Total volume of WML was quantified.

Cognitive function evaluation

Participants were evaluated for dementia **at the XX Alzheimer's Disease Center** using the National Alzheimer's Coordinating Center's Uniform Data Set (UDS) neuropsychological test battery scale employed by the United States Alzheimer's Disease Center (ADC) network.[22,23] This allows for collaboration, standardized data collection and longitudinal studies across the ADC network.[24–26] We calculated cognitive domain scores for executive function, language, processing speed, and attention normalized to a cognitively normal sample of older adults as previously reported.[27] During the study, the National Alzheimer's Coordinating Center modified their battery of tests and this resulted in the inability to maintain uniform testing across all participants, particularly in the memory domain.

Consequently, we used only the tests common to both batteries, and the summed free recall of the Free and Cued Selective Reminding Test[28] for memory domain of all participants which our site had been additionally administering to all participants. We normalized this memory domain to a similar population.[29]

Statistical analysis

Data was assessed for normality **using Shapiro-Wilk** and appropriate statistical analyses were conducted. To examine differences between individuals having a low ASCVD risk (ASCVD score <7.5%) and those having an elevated ASCVD risk (ASCVD score ≥7.5%),[13] **Welch's t-test, Wilcoxon Rank Sum test or Test of Proportions** were performed. To evaluate the influence of ASCVD risk on resting and exercise $MCAv_{mean}$, linear regressions were used.

Age is an important covariate of $MCAv_{mean}$. However, age was not adjusted for in these initial linear regression models due to its large contribution to the ASCVD risk score.[13] We did perform a sub-analysis to evaluate these linear regression models adjusting for age. Furthermore, race was not included in the analysis of the ASCVD risk score subcomponents secondary to the entire study sample identifying as white, non-Hispanic. To examine the relationship between $MCAv_{mean}$ and WML, both simple linear regressions and linear regression models adjusting for ASCVD risk were used. Additionally, linear regressions adjusted for age, gender and education were used to evaluate the relationship between $MCAv_{mean}$ and cognitive function. All data analysis were performed in Stata 15 (StataCorp; LLC,College Station, Texas, USA).

Results

Participant characteristics

Eighty-five participants enrolled in the present study and seventy-two participants had complete data sets for the primary analysis. Reasons for incomplete datasets and not **being** included in the analyses were: Missing cholesterol values (n=9) and either an unobtainable MCAv signal or artifact during exercise (n=4). Resting and exercise MCAv data for participants (n = 20) in the present study has also been previously published.[11] Participants were educated, white non-Hispanic (100%) females (69%) with a mean age of 70.0 (SD= 4.7) (Table 1). All participants identified as being physically inactive[30] and had varying levels of WML (M=2.72, SD=3.04). Nine participants were taking beta blockers and 8 reported taking calcium channel blockers. All participants reached the target HR range using the appropriate estimated HR equations. Participants had no history of cerebrovascular disease by clinical presentation and MRI.[1]

Relationship of CVD risk on MCAv

Evaluating differences between individuals having a low ASCVD risk (ASCVD score <7.5%) and those having an elevated ASCVD risk (ASCVD score ≥7.5%) revealed between group differences. Participants with an elevated CVD risk had significantly lower resting and exercise $MCAv_{mean}$. We report a significant difference in resting $MCAv_{mean}$ between those with a low ASCVD risk (M=53.95cm/s, SD=8.27) and whose with an elevated ASCVD risk

(M=44.79cm/s, SD=11.00); t(40.8)= 3.72, p=0.001. Similarly, exercise $MCAv_{mean}$ was significantly different between individuals characterized as low ASCVD risk (M=62.12cm/s, SD=11.93) and those with an elevated ASCVD risk (M=50.43cm/s, SD=11.53); t(29.6)= 3.63, p=0.001. Resting and exercise MAP and $P_{ET}CO_2$ were not different (see Table 1)

Resting $MCAv_{mean}$ significantly decreased on average by 0.43 cm/s ($\mathbf{r}^2$= 0.124, P=0.002) for every unit increase in ASCVD score (Figure 1). Exercise $MCAv_{mean}$ significantly decreased on average by 0.55 cm/s ($\mathbf{r}^2$=0.153, P=0.001) for every unit increase in ASCVD score (Figure 1). In the sub-analysis, adjusting these models for age revealed resting $MCAv_{mean}$ decreased on average by 0.47 cm/s ($\mathbf{r}^2$=0.124, P=0.046) for every unit increase in ASCVD score while exercise $MCAv_{mean}$ decreased by 0.58 cm/s ($\mathbf{r}^2$=0.153, P=0.027) for every unit increase in ASCVD score.

Evaluating the subcomponents of the ASCVD score showed that age influenced resting $MCAv_{mean}$. For every additional year, resting $MCAv_{mean}$ decreased by 0.64 cm/s ($\mathbf{r}^2$=0.072, P=0.022) and exercise $MCAv_{mean}$ decreased by 0.81 cm/s on average ($\mathbf{r}^2$=0.091, P=0.010). Males had a significantly lower resting $MCAv_{mean}$ by 5.70 cm/s compared to females ($\mathbf{r}^2$=0.571, P=0.043,). Individuals with diabetes exhibited a lower resting $MCAv_{mean}$ by 17.79 cm/s ($\mathbf{r}^2$=0.071, P=0.024,) and exercise $MCAv_{mean}$ was blunted by 17.46 cm/s ($\mathbf{r}^2$=0.052, P=0.053) on average compared to those without diabetes. No other ASCVD risk subcomponent was associated with $MCAv_{mean}$ (Table 2).

MCAv and ASCVD score with WML

Neither resting $MCAv_{mean}$ (β= −0.03 cm/s, $\mathbf{r}^2$=0.008, P=0.468) nor exercise $MCAv_{mean}$ (β= −0.02 cm/s, $\mathbf{r}^2$=0.004, P=0.595) were associated with WML (n= 66). Models adjusting for ASCVD risk score did not alter associations between resting or exercise $MCAv_{mean}$ and WML. These adjusted models revealed that ASCVD risk score was significantly associated with WML. Further investigation demonstrated for every unit increase in ASCVD risk score, WML increased by 0.10 mL ($\mathbf{r}^2$=0.082, P=0.020). This relationship was maintained after a sensitivity analysis removing outliers.

MCAv and cognitive function

Adjusting models for age, education and gender revealed that language processing was significantly associated with both resting and exercise $MCAv_{mean}$. Language processing significantly increased by 0.02 for every cm/s increase in resting $MCAv_{mean}$ ($\mathbf{r}^2$=0.077, P=0.036) (Figure 2) and by 0.02 for every cm/s increase in exercise $MCAv_{mean}$ (r^2=0.106, P=0.011) (Figure 2).

Adjusting models for age, education and gender revealed that executive function was not significantly associated with resting $MCAv_{mean}$ (β= −0.004 cm/s, $\mathbf{r}^2$=0.042, P=0.727) or exercise $MCAv_{mean}$ (β= −0.009 cm/s, $\mathbf{r}^2$=0.058, P=0.264). Adjusting models for age, education and gender revealed that memory was not associated resting $MCAv_{mean}$ (β= 0.01 cm/s, $\mathbf{r}^2$=0.098, P=0.243) or exercise $MCAv_{mean}$ (β= 0.02 cm/s, $\mathbf{r}^2$=0.116, P=0.100). Adjusting models for age, education and gender revealed that processing speed was not associated with resting $MCAv_{mean}$ (β= −0.004 cm/s, $\mathbf{r}^2$=0.069, P=0.351) or exercise

$MCAv_{mean}$ (β= 0.0008 cm/s, $\mathbf{r}^2$=0.057, P=0.835). Similarly, attention was not associated **with** resting $MCAv_{mean}$ (β= 0.01 cm/s, $\mathbf{r}^2$=0.056, P=0.492) or exercise $MCAv_{mean}$ (β= 0.01 cm/s, $\mathbf{r}^2$=0.069, P=0.229).

Discussion

The present investigation resulted in several novel findings. First, older adults characterized as non-demented and "healthy brain aging" (no cerebrovascular disease such as stroke and non-elevated for beta amyloid) with higher ASCVD risk had blunted resting and exercise $MCAv_{mean}$ than those with lower ASCVD risk. Second, resting and exercise $MCAv_{mean}$ were not associated with WML. However, WML volume was associated with ASCVD risk, such that individuals with a higher ASCVD risk had a higher WML. Third, higher resting and exercise $MCAv_{mean}$ was associated with language processing skills but not with other measures of cognition. These results extend the current evidence and highlight those with higher CVD risk have reduced MCAv during exercise, which may be an indicator of cerebrovascular health.[3,31–35]

CVD risk and MCAv

$MCAv_{mean}$ during rest provides valuable information **for establishing a baseline**. However, the addition of exercise $MCAv_{mean}$ provides a much more comprehensive evaluation of MCAv response to a physical demand. Exercise is a physiological challenge to the cerebrovasculature due to increases in cardiac output, MAP, and sympathetic nervous system activity.[36,37] Thus, evaluating the response of $MCAv_{mean}$ to exercise provides a unique assessment of cerebrovascular control[12] and perhaps could be used to characterize the risk and progression of poor brain health.

Further, there is evidence to suggest that lower resting cerebral blood flow velocity is associated with similar measures of CV risk. The Framingham General Cardiovascular Risk Profile was related to lower resting $MCAv_{mean}$ in 160 healthy adults with a mean age of 59 (n=160).[4] Similarly, another study reported a higher Framingham Risk Score was associated with lower resting cerebral blood flow using MRI techniques in large dataset (n = 576) of adults with a mean age of 46 years.[3] The present study extends the current scientific knowledge by adding an exercise challenge to the MCAv assessment. Similar to rest, we report higher ASCVD score resulted in a lower exercise $MCAv_{mean}$, further supporting the importance of maintaining cardiovascular health. Additionally, when comparing individuals having a low ASCVD risk (ASCVD score <7.5%) and those having an elevated ASCVD risk (ASCVD score ≥7.5%) we found that those with an elevated risk had significantly lower resting and exercise $MCAv_{mean}$. Overall, the results of the present study provide support that CVD risk influences $MCAv_{mean}$. We provide evidence that rest and exercise $MCAv_{mean}$ is blunted in those with elevated ASCVD risk and the importance of monitoring CVD risk for optimal brain health.

In addition to the ASCVD risk score, the present study assessed the ASCVD subcomponents to ascertain whether specific components were driving the relationship between the ASCVD score and resting and exercise $MCAv_{mean}$. The findings of the present study revealed that age, gender, and diabetes were associated with either resting or exercise $MCAv_{mean}$. These

results are consistent with studies reporting that individuals who are older, male and diabetic have suboptimal cerebrovascular health.[38–41] Given the current emphasis on cerebrovascular health and chronic disease, we provide support for the perspective that individuals with diabetes may be at risk for cerebrovascular dysfunction. Although only 2 participants had a diagnosis of diabetes, we found these individuals had a significantly lower resting (−17.8 cm/s) and exercise $MCAv_{mean}$ (−17.5 cm/s) compared to those without diabetes. Several mechanisms could explain our findings in these 2 participants. Diabetes is associated with increased blood viscosity which impairs blood flow, thereby reducing cerebral blood flow.[42–44] Hyperglycemia results in a loss of vessel elasticity, which has been linked to reduced cerebral blood flow.[45–47] Additionally, diabetes has a high prevalence of hypertension,[48] which is known to result in both structural and functional cerebrovascular alterations, such as hypertrophy and remodeling of the cerebrovasculature, increases in resistance, impaired functional hyperemia (neurovascular decoupling) and reductions in cerebral blood flow.[49] Targeting therapeutic and lifestyle interventions to reduce ASCVD risk, especially those at greatest risk for diabetes, is likely to be very important given the association between diabetes and dementia.[50] Thus, further research in this area is warranted to elucidate the mechanisms contributing to reduced resting and exercise $MCAv_{mean}$ in people with diabetes.

ASCVD Risk, cerebrovascular regulation and WML

Current evidence suggests that lower cerebral blood flow and blunted cerebrovascular regulation are associated with WML.[38,51,52] However, our results with $MCAv_{mean}$ did not support the hypothesis that these measures would be associated with higher WML. This discrepancy may be due to differences in methodology. In the present study, we assessed resting and exercise $MCAv_{mean}$ and not cerebrovascular regulation. Previous studies used MRI and acetazolamide administration to measure cerebral blood flow response. These different methods could lead to different results and thus further research is needed. We believe that exercise provides a unique physiologic challenge to the human system and **provides** insight into the interconnection between cerebrovascular health and dysfunction.[12] Exercise has great ecological validity as it is clinically prescribed and is recommended that healthcare providers assess and promote physical activity.[53] Although not a primary aim of the study, higher ASCVD score was associated with a higher WML. This is consistent with previous work demonstrating that CVD risk factors are positively associated with WML[39,54] and underscore the importance to minimize CVD risk factors across the lifespan.

MCAv and cognitive function

Reduced cerebral blood flow is associated with cognitive decline and an increased risk for stroke and Alzheimer's disease.[55] Our results partly support the association between reduced $MCAv_{mean}$ with cognitive function. We found resting and exercise $MCAv_{mean}$ to be associated with reduced language processing. Prior work has reported cerebrovascular regulation to be associated with overall cognitive function and other cognitive domains.[12,56,57] These differences may, in part, be due to cognitive assessments, participant demographics or our methodology as we didn't directly assess cerebrovascular regulation. Our participants were well-characterized cognitively normal older adults and at lower risk of developing AD as evidenced by non-elevated beta-amyloid levels, which likely affected the relationship between resting and exercise $MCAv_{mean}$ and cognition. The cohort underwent

standardized cognitive evaluation using the UDS neuropsychological test battery and the CDR, providing a rich, standardized cognitive profile and reducing the risk of contamination of our sample by prodromal dementia.[22,23] This allowed us to explore the specific contribution of CVD risk factors to resting and exercise $MCAv_{mean}$ and cognitive function.

Study participants self-identified as white, non-Hispanic, which limits the interpretation of results to individuals from other racial and ethnic backgrounds who may be at higher risk for CVD and have differing cardiac risk factors. Additionally, study participants were mostly female, which could have affected our results, given the known sex differences in MCAv.[58] As in our prior work, we have acknowledged TCD is an indirect measure of cerebral blood flow and does not account for changes in vessel diameter.[59] Though it's been reported that vessel diameter does not change,[60] this has not been unequivocally established.[61,62] **Moreover, c**holesterol values were collected during clinic visit and not drawn at the same visit as the MCAv experimental protocol, which could alter the ASCVD score. Finally, it would have been preferable to maintain a complete and consistent cognitive battery throughout the study. However, as noted in this manuscript, norming was performed either through a published UDS normative calculator or, in the case of the Free and Cued Selective Reminding Test, to a separate age, sex, education appropriate population of individuals from our prior work.[29] Finally, we must acknowledge the r-square values are small which suggests that the variables are not accounting for much of the explained variability. Future research should explore other potential variables that may influence brain health.

Considerations for Clinical Practice

The findings presented here highlight the importance of maintaining heart health for brain health. This topic is timely as we observe increased life expectancy and the occurrence of non-communicable diseases is projected to rise.[63] A timely publication by the American Heart Association, *Defining Optimal Brain Health in Adults*, strongly recommends humans minimize CVD risk factor across the lifespan to maintain both cardiovascular and brain health.[64] As physical therapists, we should regularly evaluate our patients CVD risk using several metrics (blood pressure, diet, body weight and exercise) and educate patients on CVD risk management that are optimal for heart and brain health. These findings add to a growing body of evidence that the ASCVD score has potential clinical utility to assess CVD risk either through the downloadable applications or adapting the "medical record using patient data and published equations."[13] However, further characterization about the relationship between resting and exercise $MCAv_{mean}$ and ASCVD score, including longitudinal studies are necessary.

Conclusions

Individuals with elevated ASCVD risk present with blunted resting and exercise $MCAv_{mean}$ compared to those with lower ASCVD risk. We report that specific subcomponents of ASCVD risk was associated with blunted resting and exercise $MCAv_{mean}$. Finally, resting and exercise $MCAv_{mean}$ was associated with reduced language processing. While these results suggest CVD risk management may be important for optimal brain health, more research is needed to examine other factors that may influence CVD health.

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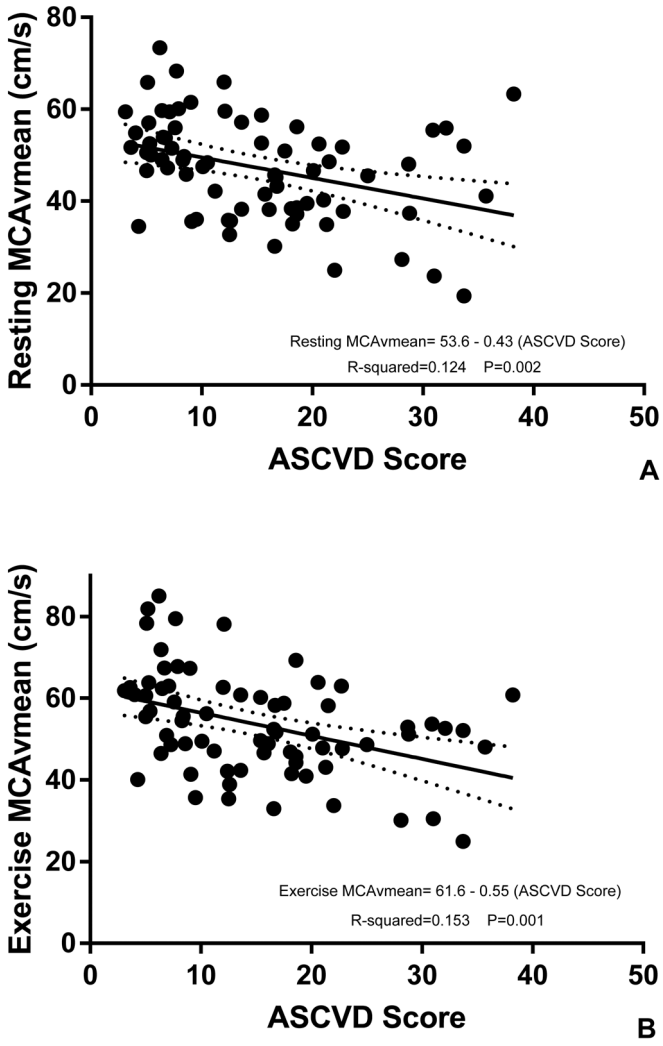

Figure 1. Associations between ASCVD Risk Score and MCAvmean;

(A) resting MCAvmean and (B) exercise MCAvmean. *P* values, R2 values and regression equations are from simple linear regression models evaluating the influence of CVD risk on cerebrovascular regulation.

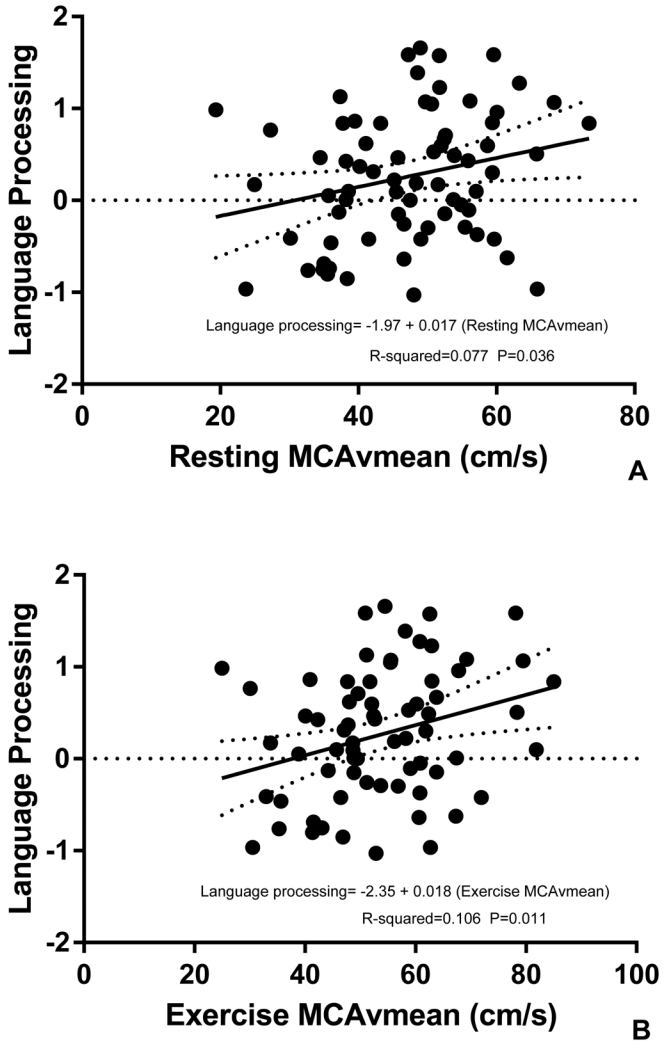

Figure 2. Associations between MCAvmean and Language Processing (normed z-scores); (A) resting MCAvmean and (B) exercise MCAvmean. *P* values, R2 values and regression equations are from linear regression models evaluating the relationship of cerebrovascular regulation and language processing adjusting for age, education and gender.

Table 1.

Participant Characteristics

Demographics	**Overall (n=72)**	**Elevated ASCVD risk (n=54)**	**Low ASCVD risk (n=18)**	**P-value**
Age (years)	70.0 (4.7)	**71.3 (4.7)**	**66.3 (1.5)**	**<0.0001**
Female (%)	69	**59.3**	**100**	**0.001**
White non-Hispanic (%)	100	**100**	**100**	-----
Education (years)	16.8 (2.5)	**16.5 (2.4)**	**17.7 (2.3)**	**0.076**
BMI (kg/m2)	26.7 (4.4)	**27.4 (4.6)**	**24.8 (2.8)**	**0.015**
Cardiovascular Disease Risk Characteristics				
ASCVD Score	15.0 (9.0)	**18.2 (8.2)**	**5.5 (1.2)**	**<0.0001**
Systolic Blood Pressure (mmHg)	131.0 (15.0)	**134.4 (14.2)**	**120.6 (13.1)**	**0.001**
Total Cholesterol (mmol/L)	190.2 (35.3)	**185.9 (35.2)**	**203.3 (33.3)**	**0.066**
HDL Cholesterol (mmol/L)	60.0 (18.1)	**58.2 (17.7)**	**65.4 (19.0)**	**0.123**
Blood Pressure Treatment %	31.0	**40.7**	**0**	**0.001**
Diabetes %	3.0	**3.7**	**0**	**0.408**
Smoking Status %	1.4	**1.9**	**0**	**0.561**
Resting and Exercise Parameters				
Resting $MCAv_{mean}$ (cm/s)	47.1 (11.1)	**44.8 (11.0)**	**53.9 (8.3)**	**0.001**
Exercise $MCAv_{mean}$ (cm/s)	53.4 (12.6)	**50.4 (11.5)**	**62.1 (11.9)**	**0.001**
Resting Mean Arterial Pressure (mmHg)	73.5 (12.6)	**74.1 (10.4)**	**71.8 (17.8)**	**0.129**
Exercise Mean Arterial Pressure (mmHg)	106.3 (20.9)	**105.6 (18.8)**	**108.1 (26.8)**	**0.792**
Resting CO2 (mmHg)	33.9 (5.2)	**33.4 (5.2)**	**35.4 (5.1)**	**0.071**
Exercise CO2 (mmHg)	37.9 (4.5)	**37.5 (4.3)**	**39.1 (4.8)**	**0.183**
Cognitive Domains				
Processing Speed	0.012 (0.397)	**−0.015 (0.421)**	**0.092 (0.312)**	**0.257**
Executive Function	−0.172 (0.816)	**−0.103 (0.886)**	**−0.377 (0.523)**	**0.156**
Language Processing	0.265 (0.705)	**0.243 (0.725)**	**0.331 (0.653)**	**0.634**
Attention	−0.214 (0.828)	**−0.253 (0.795)**	**−0.097 (0.934)**	**0.558**
Memory	0.592 (0.924)	**0.546 (0.964)**	**0.728 (0.802)**	**0.435**

Data are presented as mean (standard deviation). BMI indicates body mass index. ASCVD score indicates atherosclerotic cardiovascular disease. MCAv indicates mean middle cerebral artery blood flow velocity. Cognitive domain scores are normalized.

Table 2.

β Coefficients for Cardiovascular Disease Risk and MCAv Characteristics

	Resting $MCAv_{mean}$	**Exercise $MCAv_{mean}$**
ASCVD Score	−0.43 (P=0.002) **	−0.55 (P=0.001) **
Age	−0.64 (P=0.022) *	−0.81 (P=0.010) *
Gender	−5.70 (P=0.043) *	−4.82 (P=0.136)
Total Cholesterol	0.04 (P=0.284)	0.05 (P=0.262)
HDL Cholesterol	0.10 (P=0.159)	0.12 (P=0.133)
Systolic Blood Pressure	−0.08 (P=0.370)	−0.16 (P=0.106)
Blood Pressure Treatment	−0.89 (P=0.756)	−2.52 (P=0.437)
Diabetes	−17.79 (P=0.024) *	−17.46 (P=0.053)
Smoking	−11.70 (P=0.297)	−12.17 (P=0.342)

* P<0.05,

** P<0.01. ASCVD score indicates atherosclerotic cardiovascular disease. SBP indicates systolic blood pressure. BP indicates blood pressure. $MCAv_{mean}$ indicates mean middle cerebral artery blood flow velocity. β Coefficients are from individual simple linear regressions of MCAv values with ACSVD score and its subcomponents.