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Standing middle cerebral artery velocity predicts cognitive function and gait speed in older adults with cognitive impairment, and is impacted by sex differences

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ABSTRACT

Upright posture challenges the cerebrovascular system, leading to changes in middle cerebral artery velocity (MCAv) dynamics which are less evident at supine rest. Chronic alterations in MCAv have been linked to hypoperfusion states and the effect that this may have on cognition remains unclear. This study aimed to determine if MCAv and oscillatory metrics of MCAv (ex. pulsatility index, PI) during upright posture are i) associated with cognitive function and gait speed (GS) to a greater extent than during supine rest, and ii) are different between sexes.

Beat-by-beat MCAv (transcranial Doppler ultrasound) and mean arterial pressure (MAP, plethysmography) were averaged for 30-seconds during supine-rest through a transition to standing for 53 participants (73±6yrs, 17 females). While controlling for age, multiple linear regressions predicting MoCA scores and GS from age, supine MCAv metrics, and standing MCAv metrics, were completed. Simple linear regressions predicting Montreal Cognitive Assessment (MoCA) score and GS from MCAv metrics were performed separately for females and males. Significance was set to $p < 0.05$.

Lower standing diastolic MCAv was a significant ($p = 0.017$) predictor of lower MoCA scores in participants with mild cognitive impairment, and this relationship only remained significant for males. Lower standing PI was associated with slower GS ($p = 0.027$, $r = -0.306$) in both sexes. Our results indicate a relationship between blunted MCAv and altered oscillatory flow profiles during standing, with lower MoCA scores and GS. These relationships were not observed in the supine position, indicating a unique relationship between standing measures of MCAv with cognitive and physical functions.

Introduction[2]

The pathophysiology of dementia is multifactorial, and reduced cerebral perfusion is a significant predictor for the development and progression of dementia and may be a surrogate biomarker for cognitive impairment[1–7]. Reductions in middle cerebral artery blood flow velocity (MCAv), and changes in the oscillatory nature of MCAv, are associated with reduced cognitive function in older adults with

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[1] Shared senior authorship.
[2] CNT cognitively intact controls, MCI mild cognitive impairment, DEM dementia, MCAv middle cerebral artery velocity (suffix in replace of 'v': mv-mean, sv-systolic, dv-diastolic, pv-pulse amplitude), PI pulsatility index, RI resistance index, ETCO2 end-tidal carbon dioxide, Hb relative hemoglobin content (oxygenated OxHb, deoxygenated DeoxHb, and total TotHb), MoCA Montreal Cognitive Assessment

Alzheimer's Disease (AD) and mild cognitive impaired (MCI)[8]. The underlying mechanisms are thought to arise from a combination of changes in cerebral vasculature, reductions in elastic compliance and cellular changes within the brain[9–11]. The prevailing body of research on cerebral blood flow and dementia has been completed in the supine position when the brain and heart are within the same horizontal plane [12–15] and the gravitational challenge to the cerebral vasculature is minimized. During a change in posture from supine to standing, the cardiovascular and cerebrovascular systems must counter gravitational forces as well as a net redistribution of blood volume to the working muscles. Controversy exists in the literature regarding the relationship between orthostatic hypotension and the development of dementia [16–19]; assessing cerebral blood flow during a supine to stand transition may elucidate some of the conflicting evidence and prove to be a more sensitive measure than blood pressure (BP) in risk stratification for dementia.

During changes in posture from supine to standing or walking, 20 % of community-dwelling older adults experience a substantial reduction in blood pressure[20] and cerebral tissue saturation (tSO_2)[21], which has been associated with postural instability[22] and altered gait dynamics have been linked to lower MCAv during walking[23]; assessing cerebral perfusion in the standing position may expose clinically relevant predictors of dementia and frailty, which may not be evident at supine rest.

Slow gait speed (GS) is associated with adverse outcomes[24] and declining executive function irrespective of baseline cognitive impairment[25]. The slowing of GS precedes cognitive decline[26] by up to 12-years[27] and has been suggested to be an easily attainable and non-invasive marker for cognitive decline[26]. We propose to investigate if standing MCAv metrics are associated with GS to identify a potential mechanistic factor (e.g. cerebral perfusion) contributing to cognitive impairment[27]. Furthermore, separating the MCAv waveform into distinct functional characteristics (ex. end-diastolic velocity, *MCAdv*, or calculating pulsatility index, *PI*) may elicit a more in-depth evaluation of morphological properties associated with cerebral hypoperfusion which may otherwise be masked by means and data smoothing.

Unique to this experiment is to test the hypothesis that standing cerebral perfusion, compared to supine cerebral perfusion, is a more sensitive marker of cognitive ability and motor task performance. In this report, we studied dynamic changes in MCAv and the decompressed velocity profiles against indices of cognition and GS, in a cohort of older adults to test if declining cognition in older adults associates with standing components of MCAv. More specifically, we hypothesized that participants with lower standing MCAv and greater oscillatory components of the MCAv waveform would have lower MoCA scores and slower gait speeds, and that this relationship would be predominant in participants with mild cognitive impairment (MCI) and dementia (DEM) and absent in cognitively intact controls (CNT) and at supine rest. We also explored sex-based differences in these relationships, and we hypothesized that males and females would demonstrate different associations between lower MCAv and lower MoCA scores.

Methods

Study participants were recruited from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) Study at the Parkwood Institute location in London, ON. The COMPASS-ND Study is a Canadian cohort research initiative, and it is a clinical study within the Canadian Consortium on Neurodegeneration in Aging (CCNA). All procedures were reviewed and approved by Clinical Trials Ontario (CTO750) at Western University and conformed with the Declaration of Helsinki. Informed written consent was obtained for all participants, after which nonidentifiable identification were generated to ensure the privacy of all participants. Specific study inclusion and exclusion criteria, participant selection, clinical group ascertainment, data

acquisition, and data processing have previously been published[28, 29]. Participants were separated into three groups, i) cognitively intact controls (CNT), ii) mild cognitive impairment (MCI), and iii) dementia (DEM). Briefly, participants were considered CNT if they had normal cognition or subjective cognitive impairment[29], as demonstrated by the fulfillment of the following criteria: a Global Clinical Dementia Rating (CDR) equal to zero[30], verbal memory assessed with Logical Memory (with education adjusted cut-offs)[31], Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[32], a word list recall score greater than five words or greater than six words on the Rey Auditory Verbal Learning-trail 7, and a total MoCA score greater than 24[28,29]. Classification criteria for MCI included the National Institute on Aging, Alzheimer's Association Clinical Criteria[33], a self-reported concern of changes in cognitive function, preserved independence marked by a score of greater than 14 on the Lawton and Brody Scale, absence of dementia based on a CDR score less than 1, and the impairment in one or more of the following, Alzheimer's Disease Neuroimaging initiative, CERA, a MoCA score less than 24, or a CDR score of 0.5[28,33]. Participants with a diagnosis of Alzheimer's disease ($n = 3$), vascular cognitive impairment ($n = 9$), and mixed vascular and Alzheimer's dementia ($n = 4$) were included in a single dementia group (DEM)[28,33].

The study sample consisted of 88 participants, where 35 participants were excluded from final analysis due to inadequate MCAv signal acquisition through the supine-to-stand transition [28,29]. Transcranial Doppler ultrasound (TCD-X; Atys medical, Soucieu en Jarrest, France) was used to collect MCAv metrics. Different components of the MCAv waveform were studied including (peak-systolic: MCAsv, MCAdv, and mean: MCAmv), whereas cerebrovascular resistance (CVRi=mean arterial pressure at MCA/MCAmv), MCAv pulse-amplitude (MCApv=MCAsv-MCAdv), PI (MCAsv-MCAdv/MCAmv), and resistance index (RI= MCAsv-MCAdv/MCAsv) were calculated. End-tidal carbon dioxide ($ETCO_2$) was collected using a gas analyzer (Capnostream 35, Medtronics, USA and Ireland). Near-infrared spectroscopy (NIRS; Artinis Medical Systems BV, Netherlands) was used to collect tSO_2 and relative changes in oxygenated, deoxygenated, and total hemoglobin content (OxHb, DeoxHb, TotHb, respectively) and differences between OxHb and DeoxHb (DiffHb).

Statistical analysis

Data were analyzed using SPSS software (version 26, IBM Corp, Armonk, NY, 2019). After testing for normality (Shapiro-wilk), analyses were completed with the assumption of having normally distributed data. All participants were grouped by cognitive category (CNT, MCI,

Table 1
Participant characteristics separated by clinical group.

Characteristic	CNT, $n = 14$	MCI, $n = 30$	DEM, $n = 9$	p-value and phi
Female,%	50	33	0	*P* = 0.042, phi=0.346
Age, years	72±6	74±6	80±6 **† ‡	*p* = 0.005
BMI, kg/m²	28±5	26±4	27±3	N.S.
Education years, avg ±SD	16±3	17±4	16±4	N.S.
MoCA score out of 30	27±2	24±4	19±6**† ‡	*p*<0.001
Gait speed, m/s	1.22 ±0.26	1.15 ±0.23	0.98±0.19*†	*p* = 0.057
Total path length (cm)	2.06 ±0.31	2.27 ±0.56	3.10 ±0.74**† ‡	*p* = 0.001
On BP lowering meds, n,%	6, 43	6, 20	6, 67**	*p* = 0.026, phi=0.373

CNT control group, *MCI* mild cognitive impairment group, *DEM* group with dementia, *BMI* body mass index, *MoCA* Montreal Cognitive Assessment, *BP* blood pressure, *$*p \leq 0.1$ (trend), ** $p \leq 0.05$, post-hoc: † $p \leq 0.05$ vs. CNT, ‡ $p \leq 0.05$ vs. MCI.

DEM). Chi-square testing was used for categorical variables and one way ANOVA testing was used for continuous variables (Table 1). Correlations between all cardio- and cerebrovascular measures were calculated using partial Pearson correlations while controlling for age. Predictive modelling using multiple linear regressions including age, a supine vascular measure and the corresponding standing vascular measure was applied to the MCI group (Fig. 2). Due to sample size limitations, only two predictors (age and a supine vascular measure, or age and a standing vascular measure) were applied the to multiple linear regression analysis of the CNT group. A variance inflation factor was used to detect multicollinearity between metrics. Predictive modeling using simple linear regression in females and males separately was used to identify sex differences. A two-way repeated-measures ANOVA was performed to determine group differences (CNT, MCI, and DEM), the effects of position (supine and 1-minute standing), and the interaction of group by position (Table 2). A Bonferroni correction factor was applied, and Tukey post-hot analysis was performed to identify group differences. Significance was defined as a p-value equal to or less than 0.05, and trends are reported as greater than 0.05 and less than 0.1.

Results

Group characteristics

Group characteristics are listed below in Table 1. Females comprised 50 %, 33 %, and 0 % of the CNT, MCI and DEM groups respectively ($p = 0.042$, phi=0.346, Table 1). Participants in the DEM group were older (80±6 years, $p = 0.005$), had lower MoCA scores (19±6, $p<0.001$) and were more likely to be on blood pressure lowering medications (67 % of DEM participants, $p = 0.026$, phi=0.373) compared to CNT and MCI participants (Table 1).

Vascular changes at supine and standing

Cardiovascular hemodynamics demonstrated a significant effect ($p<0.05$) when transitioning from supine to standing for heart rate, systolic BP, mean arterial BP, pulse pressure, BP at middle cerebral artery level, stroke volume, and cerebrovascular resistance index(Table 2, Fig. 4). There were significant between-group differences for stroke volume and cerebrovascular resistance index (Table 2). We observed significant effects when transitioning from supine to standing for all cerebrovascular measures. There were significant between-group differences observed with MCAmv and although not significant a trend ($p = 0.078$) was observed for MCAdv, with those in the dementia group demonstrating the lowest velocity at both supine and standing compared to the MCI group (Table 2, Fig. 4).

Vascular measures and cognitive scores

All cerebrovascular measures demonstrated a significant ($p<0.05$) difference between supine and standing positions; thus, we further examined if these measures were associated with MoCA-based cognitive scores. After controlling for the effects of age, supine PI and RI demonstrated a negative correlation with total MoCA scores (PI: $p = 0.02$, $r=-0.334$, RI: $p = 0.032$, $r=-0.309$, Fig. 1A). This association was also observed as a trend and a significant finding in the standing positions (PI trend: $p = 0.061$, $r=-0.273$, RI: $p = 0.05$, $r=-0.285$). There was a pronounced sex difference, where males demonstrated a significant linear relationship between MCAv metrics and MoCA scores at supine rest {PI: [$F(1,31)=10.997$, $p = 0.002$, $R^2=0.262$ $\beta=-8.937$], RI: [$F(1,31)=11.981$, $p = 0.002$, $R^2=0.279$ $\beta=-37.407$]} and during standing {PI: [$F(1,31)=5.829$, $p = 0.022$, $R^2=0.158$, $\beta= -3.937$], RI: [$F(1,31)=8.007$, $p = 0.008$, $R^2=0.205$, $\beta= -27.782$]} which were not observed in females (Fig. 1).

The same analysis was performed for all cardiovascular measures that had demonstrated a significant difference between supine and standing values. However, these cardiovascular measures did not show a significant correlation with MoCA scores.

Table 2
Cardio- and cerebrovascular hemodynamics separated by time and clinical group.

	Supine			Minute 1 Standing			Group	Position &
	CNT	MCI	DEM	CNT	MCI	DEM	Effect	Interaction Effects
Cardiovascular Hemodynamics								
Heart Rate, bpm	64.5 ± 8.1	66.6 ± 11.5	66.4 ± 10.3	76.8 ± 13.2	82.2 ± 14.7	80.1 ± 13.1		$p<0.001$
Systolic BP, mmHg	120.2 ± 15.9	124.0 ± 18.7	121.9 ± 8.2	113.9 ± 18.6	117.4 ± 23.6	112.6 ± 14.8		$p<0.001$
Diastolic BP, mmHg	64.8 ± 13.4	67.3 ± 12.4	72.8 ± 6.3	66.0 ± 13.7	69.0 ± 15.3	69.6 ± 10.0		
MAP, mmHg	85.7 ± 13.8	88.9 ± 14.2	91.3 ± 7.5	83.2 ± 14.8	87.1 ± 18.5	85.1 ± 11.5		$p = 0.045$
PP, mmHg	55.4 ± 10.5	56.7 ± 11.5	49.1 ± 3.6	47.8 ± 11.8	48.4 ± 13.7	43.0 ± 9.1		$p<0.001$
BP$_{MCA}$, mmHg	85.7 ± 13.8	88.9 ± 14.2	91.3 ± 7.5	57.1 ± 14.6	60.5 ± 18.0	58.1 ± 15.1		$p<0.001$
Qi,L/min/m^2	2.88±0.46	3.08±0.74	2.39±0.65	2.69±0.46	3.02±0.70	2.54±0.59‡	$p = 0.058$	
Svi, mL/m^2	44.1 ± 7.8	47.7 ± 10.1	35.9 ± 6.4	34.9 ± 6.8	37.8 ± 9.1	32.2 ± 7.4‡	$p = 0.035$	$p<0.001$
TPRi, mHg/L/min/m^2	8.56±3.14	8.27±2.77	10.27±2.38	9.10±2.98	8.33±3.11	9.02±2.10		
CVRi, mmhg/cm/s	1.49±0.33	1.60±0.62	2.20±0.36	1.70±0.42	1.84±0.70	2.29±0.30†	$p = 0.048$	$p = 0.004$
Cerebrovascular Hemodynamics								
MCAsv, cm/s	68.4 ± 9.1	73.2 ± 13.9	62.0 ± 15.9	67.7 ± 10.1	71.9 ± 15.6	63.7 ± 17.5		
MCAdv, cm/s	22.4 ± 5.7	22.7 ± 6.3	18.3 ± 2.9	19.5 ± 4.2	18.8 ± 5.1	15.0 ± 4.2‡	$p = 0.078$	$p<0.001$
MCAmv, cm/s	40.0 ± 7.0	41.2 ± 8.8	33.0 ± 7.4	34.4 ± 5.7	34.8 ± 6.8	29.2 ± 7.3‡	$p = 0.04$	$p<0.001$
MCAvpa, cm/s	46.0 ± 6.5	50.5 ± 11.5	43.7 ± 13.6	48.3 ± 9.8	53.1 ± 15.9	48.6 ± 17.3		$p = 0.005$
PI, cm/s	1.17±0.21	1.25±0.28	1.31±0.19	1.43±0.34	1.56±0.49	1.68±0.49		$p<0.001$
RI, cm/s	0.67±0.06	0.69±0.07	0.70±0.05	0.71±0.07	0.73±0.08	0.75±0.08		$p<0.001$
ETCO$_2$, mmHg	36.7 ± 2.0	36.9 ± 3.7*	34.2 ± 2.2*	33.7 ± 1.6	34.0 ± 3.8	33.5 ± 2.7		Int. $p = 0.049$
tSO$_2$,%	74.9 ± 2.7	72.6 ± 4.3	71.8 ± 3.8	73.2 ± 2.8	70.4 ± 4.2	71.1 ± 3.1		$p<0.001$
OxHb, μMol	0.00±0.02	−0.03±0.15	0.00±0.002	−2.88±2.03*	−2.38±1.57§	−0.51±1.79*§		Int. $p = 0.02$
DeoxHb, μMol	0.00±0.00	0.00±0.03	0.00±0.01	0.11±0.98	0.53±0.79	0.91±0.64		$p<0.001$
TotHb, μMol	0.00±0.02	−0.03±0.18	0.01±0.002	−2.77±2.78*	−1.85±2.07§	0.40±2.39*§		Int. $p = 0.023$
DiffHb, μMol	0.00±0.02	−0.02±0.12	0.00±0.001	−2.99±1.55*	−2.92±1.36§	−1.43±1.25*§		Int. $p = 0.046$

Supine −45 to −15 second average, Minute 1 Standing 30 to 60 second average, CNT control group, MCI mild cognitive impairment group, DEM cgroup with dementia, Int. interaction of group by position, BP blood pressure, MAP mean arterial pressure, BPbrain brain level blood pressure, Qi cardiac output, SVi stroke volume, TPRi total peripheral resistance, CVRi cerebrovascular resistance index, MCAv middle cerebral artery velocity (subscripts: s systolic, d diastolic, m mean), PI pulsatility index, RI resistance index, PETCO$_2$ end-tidal carbon dioxide, tSO$_2$ cerebral tissue saturation, OxHb oxygenated hemoglobin, DexHb deoxygenated hemoglobin, TotHb total hemoglobin. Group effect post-hoc groups: † vs. CNT, ‡ vs. MCI. Pairwise comparisons marked by * and §.
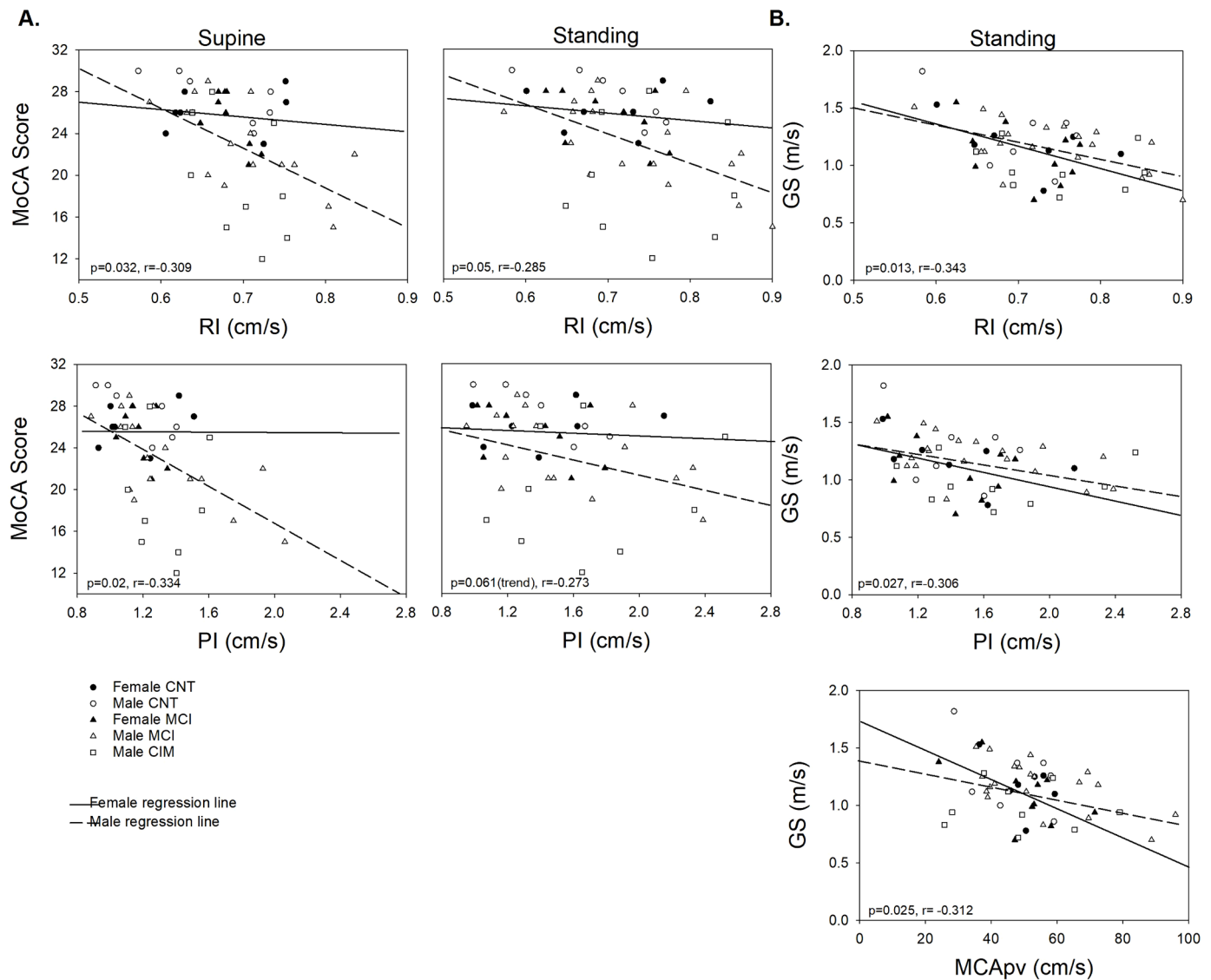
Fig. 1. Correlations between resistance index (RI), pulsatility index (PI) and middle cerebral artery velocity pulse amplitude (MCApv) with Montreal Cognitive Assessment (MoCA) scores and gait speed (GS). The p-values and r values are representative of the partial Pearson correlations controlling for age and the regression lines are simple linear regressions for females (solid line) and males (dashed line) to allow for visual comparison between sexes and among clinical cohorts of participants with dementia (DEM), mild cognitive impairment (MCI), and intact cognition (CNT). **A.** Supine and standing RI and PI are negatively associated with MoCA scores, and simple linear regression analysis reveals that males are predominantly driving this relationship. **B.** standing RI, PI and MCApv are associated with GS in females and males.

Vascular measures and gait speed

Standing PI, RI, and MCApv were significantly higher than supine values (Table 2). After controlling for age, PI, RI, and MCApv demonstrated a negative correlation with GS (all $p<0.05$, all $r=-0.3$ or less, Fig. 1B). This association was only observed during standing and not at supine rest. When separated by sex, the simple linear regression analysis between PI and GS were maintained as a trend for females [$F(1,15)=3.605$, $p = 0.077$, $R^2=0.14$, $\beta=-0.319$], and significant for males [$F(1,34)=8.194$, $p = 0.007$, $R^2=0.194$, $\beta=-0.222$] as noted in Fig. 1B. When separated by sex, simple linear regression analysis identified that the relationship between RI and GS were maintained for females [$F(1,15)=4.68$, $p = 0.047$, $R^2=0.238$, $\beta=-1.861$] and males [$F(1,34)=10.429$, $p = 0.003$, $R^2=0.235$ $\beta=-1.501$], as observed in Fig. 1B. A faster GS with lower MCApv was noted in females [$F(1,15)=6.378$, $p = 0.023$, $R^2=0.298$, $\beta=-0.012$], and males [$F(1,34)=5.366$, $p = 0.027$, $R^2=0.136$ $\beta=-0.006$] when applying a simple linear regression (Fig. 1B). In contrast, when separated by sex, simple linear regression analysis

revealed only females demonstrated a trend for faster GS with lower MCAsv during standing [$F(1,15)=3.435$, $p = 0.084$, $R^2=0.186$, $\beta=-0.008$]. Supine ETCO$_2$ was significantly and positively associated with GS ($p = 0.002$ $r = 0.459$), and standing ETCO$_2$ had a trend to be positively associated with GS ($p = 0.056$ $r = 0.294$), which was only significant in simple linear regression analysis for males [$F(1,29)=26.257$,$p<0.001$, $R^2=0.475$, $\beta=0.057$] and not females.

Differences within each clinical group

Analysis within the CNT Group: The multiple regression analysis for the CNT group examined the relationship between MoCA scores, and two predictors, i) age and ii) one hemodynamic variables. Supine TPRi was negatively and significantly associated with MoCA scores [$F(29)=4.709$, $p = 0.04$, $R^2=0.511$], and supine TPRi, not age, had a trend ($p = 0.078$) to predict the MoCA scores. Standing MCAsv had a trend ($p = 0.08$) to be negatively associated with MoCA scores [$F(2,11)=3.203$, $p = 0.08$, $R^2=0.368$], and standing MCAsv, not age, had a trend ($p = 0.075$)

to predict MoCA scores. For both supine TPRi and standing MCAsv, the coefficient of standard errors were less than the standardized co-efficients beta, suggesting the relationships were reliable despite having a sample size of $n = 14$.

Analysis within the MCI Group: Several multiple regression analyses

models were conducted in the MCI group to examine the relationship between the dependent variable, MoCA scores, and various potential predictors. The predictors, or independent variables, always included i) age, ii) a vascular measure in the supine position, and iii) the corre-sponding vascular measure in the standing position. The overall
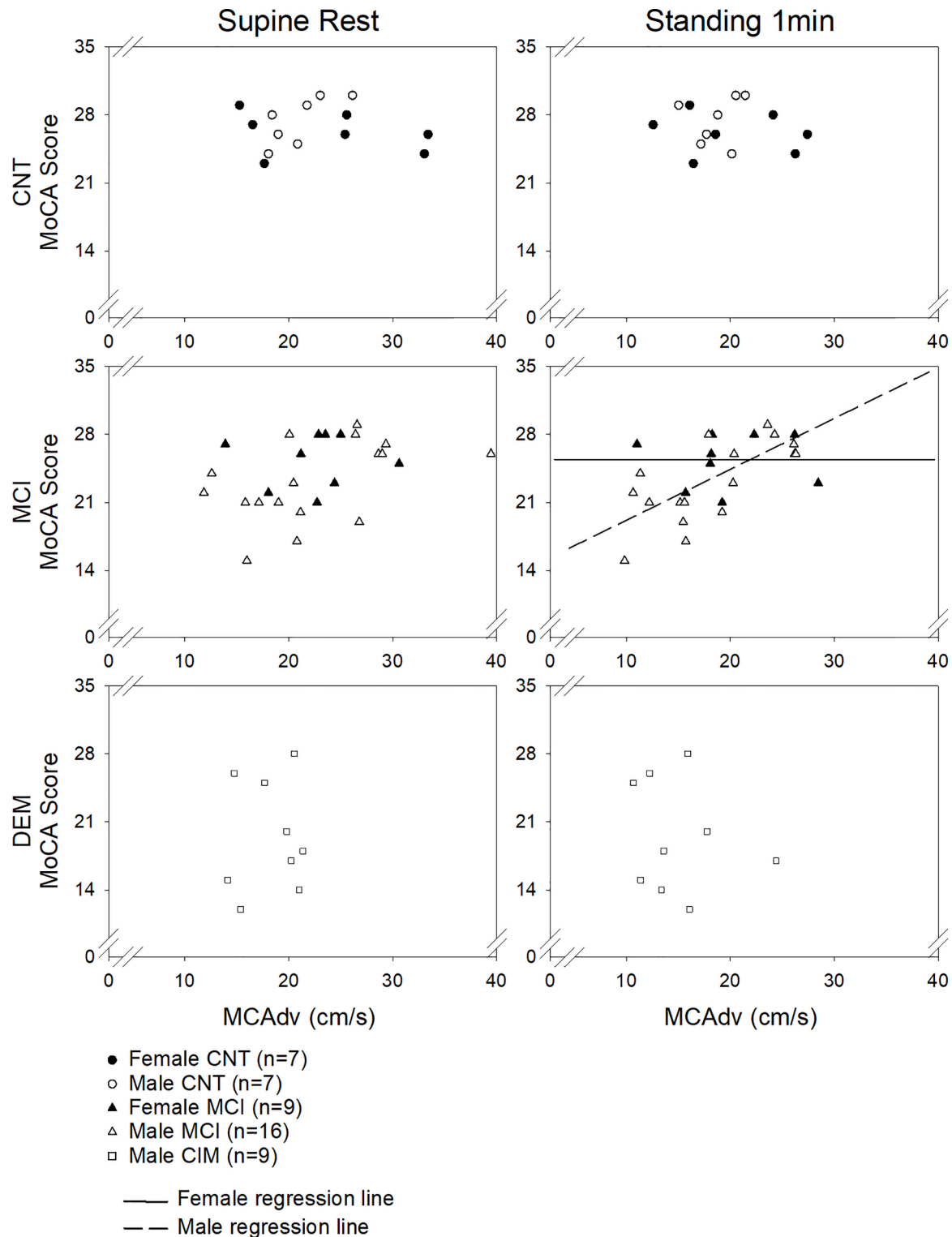

Fig. 2. **Middle cerebral artery velocity at diastole (MCAdv) and Montreal Cognitive Assessment (MoCA) scores within each clinical cohort (A) and in two age-matched males (B). A.** Supine and standing MCAdv at supine rest and during standing in controls (CNT, circles), mild cognitive impairment (MCI, triangles), and cognitive impairment (DEM, squares) for females (filled symbols and solid regression line) and males (open symbols and dashed regression line). **B.** Beat-to-beat-changes in MCAdv in two age- and sex-matched individuals during a supine to stand.

multiple regression model predicting MoCA scores, with predictors age, supine MCAdv, and standing MCAdv was significant [$F_{(3,22)}=4.207$, $p = 0.017$, $R^2=0.0365$]. Standing MCAdv added significantly to the prediction ($p = 0.044$), and for every 1 cm/s increase in MCAdv, MoCA scores increased by 0.391 (Fig. 2). When separated by sex, only males demonstrated this relationship between higher MCAdv and greater MoCA scores [$F_{(1,15)}=15$, $p = 0.001$, $R^2=0.502$, $\beta=0.512$]. The overall multiple regression model predicting MoCA scores, with predictors age, supine RI, and standing RI, was significant, [$F_{(3,22)}=5.523$, $p = 0.006$, $R2=0.43$, $\beta=-0.097$]; however none of the predictors were singularly significant. The overall multiple regression model predicting MoCA scores, with predictors, age, supine PI, and standing PI, was significant, [$F_{(3,22)}=6.450$, $p = 0.006$, $R^2=0.468$]; however none of the predictors were individually significant. Multiple regression models which significantly predicted MoCA scores included MCAsv ($p = 0.035$), and MCApv ($p = 0.009$), both with significant predictors of age to contribute to the MoCA score. Multiple regression models which had a trend to predict MoCA scores included MCAmv ($p = 0.073$), ETCO$_2$ ($p = 0.083$), TSI ($p = 0.073$), OxHb ($p = 0.067$), DeoxHb ($p = 0.067$), TotHb ($p = 0.061$), and OxHb-to-DeoxHb difference ($p = 0.073$), all of which had a significant predictor of only age to contribute to MoCA scores.

Analysis within the DEM Group: No significant results were observed.

Correlations between MoCA and GS separated by sex

While controlling for age, significant correlations were observed between MoCA and GS scores ($p = 0.018$, $r = 0.341$, Fig. 3). After separating the data set by sex and running simple linear regressions, males had associations between GS and MoCA [$F_{(1,31)}=9.810$, $p = 0.004$, $R^2=0.24$, $\beta=9.682$], and females had trends [$F_{(1,14)}=4.549$, $p = 0.051$, $R^2=0.245$ $\beta=4.968$], as observed in Fig. 3.

Discussion

This exploratory study found that MCAv changes predicted MCI and DEM. This is most pronounced in males and is distinct from standard measures of mean arterial BP. Specifically, we found i) lower standing MCAdv in MCI participants was associated with a lower MoCA score (Fig. 2), and increased standing MCAsv (trend), MCApv, RI, and PI, across a spectrum of clinical groups were associated with slower GS (Fig. 1), and ii) compared to males, females had a stronger relationship between standing RI, PI, and MCApv with GS, and a weaker association between standing MCAdv and MoCA.
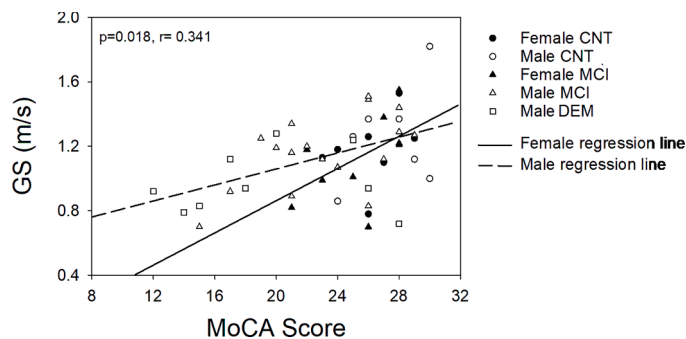

Fig. 3. Performance on the Montreal Cognitive Assessment (MoCA), gait speed (GS) and postural stability (total path length, TPL) are associated with one another in both sexes. The p-values and corresponding r values from the partial Pearson correlations (controlling for age) reflect relationships between MoCA, GS, and TPL across varying levels of cognitive function; controls (CNT), mild cognitive impairment (MCI), and dementia (DEM). The regression lines for females (solid line) and males (dashed lines) demonstrate how the relationships between outcome variables differ among the sexes.

The current study is unique because the relationships between clinical outcomes and cerebrovascular function were observed during upright posture only. At supine rest, the vascular system remains unchallenged by gravitational stress, and MCAv remains stable. Our reports of altered standing MCAsv, MCApv, PI, and RI in participants with lower MoCA scores and slower self-selected GS suggest chronic oscillatory flow profiles of the cerebral circulation to be an early potential contributor to cerebrovascular damage. Inadequate aortic buffering and disproportionate vascular stiffness between the aorta/carotid and intracranial vessels amplify the forward energy waveform, which contributes to increased systolic pressures, decreased diastolic pressure [34], and increased cerebral pulsatility[35]. We observed elevated MCAsv during standing to be negatively associated with MoCA scores and GS, which agrees with other reports of an inverse relationship between MCAsv and global cognitive decline[36]. Elevated amplitudes of forward wave energy in midlife are predictive of cognitive decline in later-life[37], and both PI[38] and RI[39] have also been associated with cognitive impairment or the progression of cognitive impairment for Alzheimer's disease and Parkinson's disease. We extended these findings to include cognitively intact and MCI participants and identified elevated PI and RI to be associated with GS.

People with MCI represent a potential clinical cohort to target and improve factors impacting cognitive decline prior to the overt progression to dementia. After separating the participants into clinical cohorts, we identified standing MCAdv as a hemodynamic index that was prominently associated with MoCA scores in MCI. MCAdv profiles indicate the lowest level of flow within a cardiac cycle and thus are most sensitive to drops in MAP. During orthostatic stress tests, adults with syncope demonstrate reductions in MCAdv without notable changes in MCAsv[40]. Similarly, previous researchers have identified significantly lower MCAdv, higher RI values, and no difference in MCAsv at supine rest in people with dementia versus cognitively intact individuals with Parkinson's disease[39]. What remains unclear is whether decreased MCAdv is a consequence of reduced metabolic demand in individuals with cognitive impairment or if altered hemodynamic function and impaired cerebral autoregulation lead to transient or chronic cerebral hypoperfusion, causing neuronal damage. Our investigation showed standing MCAdv and not age or supine MCAdv was a significant predictor of MoCA scores, suggesting changes in standing MCAdv may be an early sensitive marker of transient cerebral hypoperfusion.

Mechanisms

Elevated values of ETCO$_2$ in either supine or uprights positions were associated with a faster GS. The cerebral vasculature is highly sensitive to changes in PaCO$_2$ whereby increases in PaCO$_2$ result in cerebral vasodilation, which increases cerebral blood flow in an attempt to restabilize pH levels[41]. In the present study, the higher overall ETCO$_2$ during the supine-to-stand protocol for some individuals may have been protective in buffering against the posture-related changes of MCAv during walking[42]. Consequently, a higher ETCO$_2$ and MCAv during walking would allow for motor control centers to continue functioning optimally, and thus a self-selected faster walking pace may have resulted.

The second aim of this investigation was to study the constructs of sex differences for cerebrovascular hemodynamics. When separated by sex, females had slightly stronger relationships between amplified flow patterns and GS (Fig. 1)[11]. Males had a significant relationship between standing MCAdv and MoCA (Fig. 1). Females did not have this same relationship which may be due to a low sample size. Interestingly, both sexes have similar relationships between PI and RI with GS, yet females have a stronger relationship between MoCA scores and GS compared to males, and a weaker relationship between PI and RI with MoCA scores (Fig. 3). Improved understanding of sex-related differences in the development of dementia is critical for diagnosis and treatment of cognitive impairment, including physical therapy where the risk of falls
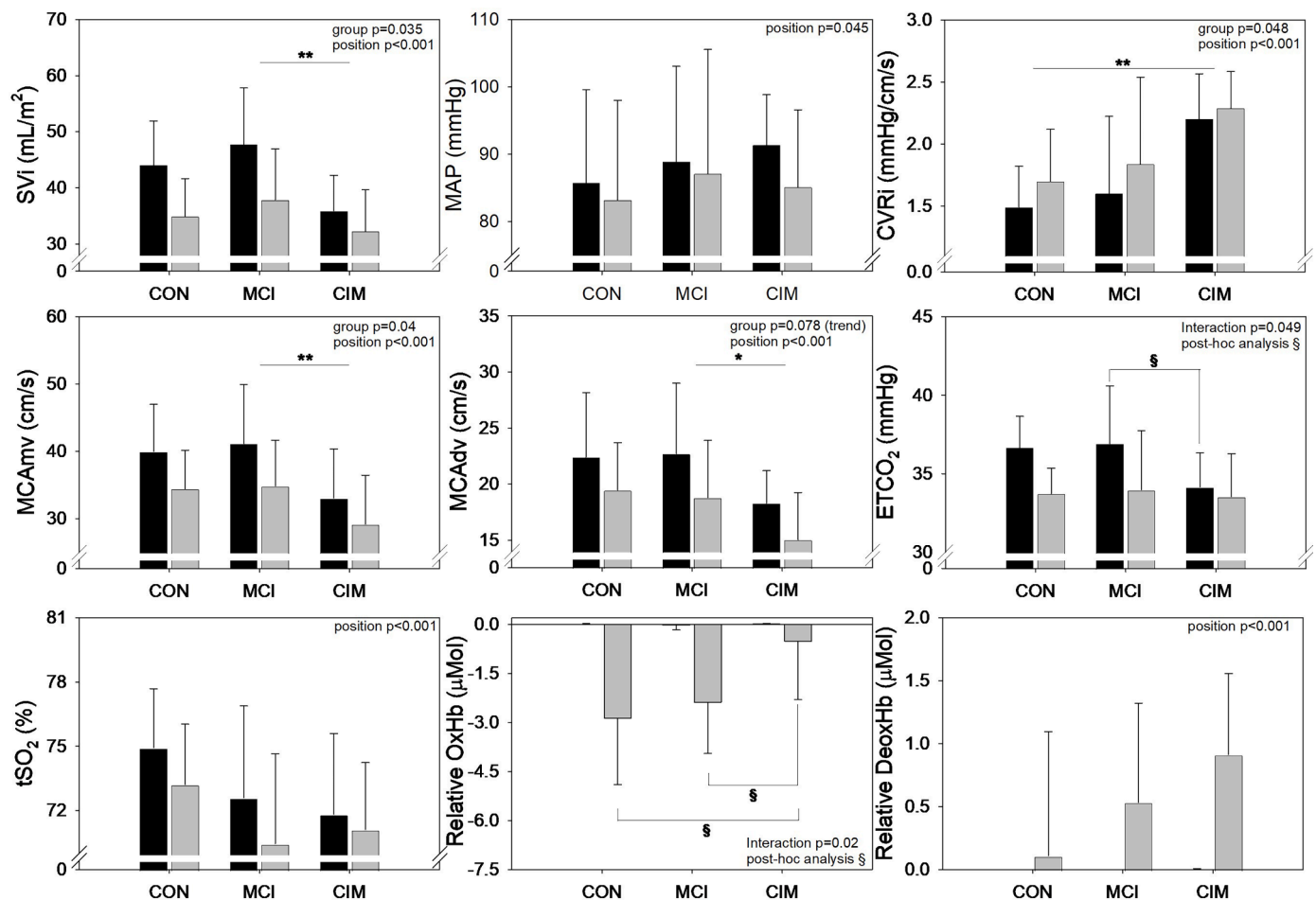
Fig. 4. Group differences and the effects of posture on hemodynamic variables. *CNT* control group, *MCI* mild cognitive impairment group, *DEM* group with dementia, *Interaction* group effect by effect of position, *SVi* stroke volume, *MAP* mean arterial pressure, *CVRi* cerebrovascular resistance index, *MCAv* middle cerebral artery velocity (subscripts: d diastolic, m mean), $ETCO_2$ end-tidal carbon dioxide, tSO_2 cerebral tissue saturation, *OxHb* oxygenated hemoglobin, *DexHb* deoxygenated hemoglobin. Group effect post-hoc ** $p < 0.05$, * $p < 0.085$ (trend). Pairwise comparisons marked by §.

becomes greater with age[43]. To better understand these relationships studies including females with a dementia diagnosis should be considered.

In reviewing group differences, the DEM group had lower stroke volume and MCAmv compared to the MCI group and a higher CVRi compared to the CNT group. There was a significant interaction for group by position for OxHb and TotHb where pairwise comparisons revealed a smaller postural reduction of OxHb in the DEM group compared to the other two clinical groups, and an increase in TotHb for the DEM group compared to CNT and MCI groups. Identifying a smaller postural reduction of OxHb and an increase in TotHb in the DEM group may initially appear as a positive outcome. However, the lower MCAmv in the DEM group with observed changes in increasing DeoxHb, suggests a disproportionate change of increased DeoxHb and reduced OxHb content.

There is conflicting evidence regarding the association of orthostatic hypotension and cognition[16–19]. We have shown that cerebrovascular measures of blood flow are a more sensitive indicator of change and have a stronger correlation with cognitive function and GS, than BP. These associations are important as treatment trials which aim to improve cerebral perfusion are lacking and often limited by the time and resource required to perform imaging studies.

Limitations

There are study limitations that should be considered, including a small sample size and the use of transcranial Doppler ultrasound to estimate changes in cerebral blood flow. The relatively small sample size in the CNT and DEM groups does not allow for multiple regression analysis with both supine and standing hemodynamic variables or the evaluation of sex differences within the same model. Yet, the results point to the need for continued focus and replication of these outcomes. Transcranial Doppler ultrasound is based on the assumption that vessel length and diameter remain constant. The changes in MCA diameter during hypo- and hypercapnia suggest an overall 0.4 % change in MCA diameter for a given change in mmHg $ETCO_2$[44]. Our participants had a -2.4 ± 2.6 mmHg $ETCO_2$ change from supine to standing, which equates to less than a 1 % change in MCA diameter. Based on these assumptions, the posture-related reductions in MCAv are slightly underestimate[39,40]. Age was included in all of the multiple linear regression models but not in the two-way ANOVA as age was known to be significantly greater in the DEM group. The MCAv values of the current study were compared to population values age-matched older adults in an effort to separate age from disease processes. Published population data for MCAmv (47.6 ± 10.1 cm/s)[45], compared to the current study (CNT: 40.0 ± 7.0 cm/s, MCI:41.2 ± 8.8 cm/) identify MCAmv values which fall within a single standard deviation of the population data. However, the DEM group MCAv average is well below a single standard deviation. The lower cerebrovascular flow profiles observed in the DEM group average (33.0 ± 7.4 cm/s) lie outside of one standard deviation of population data, and therefore, the pathophysiological process or small brain mass may be contributing to observed

changes in addition to the ageing process.

Conclusions and future directions

This study is the first to report that lower standing MCAdv was a significant predictor of lower MoCA scores for individuals with MCI, and after combining all clinical cohorts, lower standing PI, and RI were associated with slower GS. Taken together, these findings indicate several hemodynamic changes during standing are associated with a potential loss of function of motor control centers and processing regions, which are undetected at supine rest. Assessing MCAv in the upright posture may flag early changes in cerebrovascular function, which are related to neural processing unique to a standing posture.

We have identified potential drivers of sex differences in the domains of cognitive function and motor control from standing hemodynamic assessments. Males demonstrated a relationship between increased oscillatory flow profiles and lower MoCA scores, as well as lower standing MCAdv and lower MoCA scores for MCI participants. The sex differences were less evident between vascular hemodynamics and GS, as both sexes demonstrated a relationship between increased PI and RI with reduced GS. Although these study results were exploratory in nature, the findings can help form the foundation for future sex-specific investigations. The current study findings reinforce the notion that unstressed conditions do not reveal the true hemodynamic nature experienced during normal daily living.

CRediT authorship contribution statement

Laura K Fitzgibbon-Collins: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. **Geoff B Coombs:** Data curation, Writing – review & editing, Funding acquisition. **Mamiko Noguchi:** Formal analysis, Methodology, Software, Writing – review & editing. **Shashankdhwaj Parihar:** Data curation, Formal analysis. **Richard L Hughson:** Writing – review & editing, Methodology, Resources. **Michael Borrie:** Conceptualization, Supervision, Resources. **Sue Peters:** Resources, Writing – review & editing. **J Kevin Shoemaker:** Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing. **Jaspreet Bhangu:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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