Cerebrovascular function response to prolonged sitting combined with a high-glycemic index meal: A double-blind, randomized cross-over trial

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ABSTRACT

Acute prolonged sitting leads to cerebrovascular disruptions. However, it is unclear how prolonged sitting interacts with other common behaviors, including high-(HGI) and low-glycemic index (LGI) meals. Using a double-blind randomized cross-over design, this study evaluated the effects of prolonged (3 hr) sitting, with a high-(HGI; GI: 100) or low-glycemic index (LGI; GI: 19) meal on total brain blood flow (Q_{Brain}) and executive function. Eighteen young, healthy, active participants (22.6 [3.1] y, 33% F, 24.3 [3.7] kg/m2) sat for 3 hr after consuming an HGI or LGI meal. Using Doppler ultrasound to measure internal carotid (ICA)

and vertebral (VA) artery blood flow, Q_{Brain} was calculated: (ICA blood flow + VA blood flow) × 2. Executive function was assessed using the Stroop Test and Trail Making Test—Part B. Brain fog was measured using a modified Borg Category Scale with Ratio properties (CR10). Following 3 hr of sitting, there was a significant decrease in Q_{Brain} with time (p = .001, ES = −0.26), though there were nonsignificant interaction (p = .216) and condition effects (p = .174). Brain fog increased (p = .024, ES = 0.27) and Stroop reaction time worsened with time (p = .001, ES: −0.40), though there were nonsignificant condition effects for brain fog (p = .612) and the Stroop test (p = .445). There was a nonsignificant condition effect (p = .729) for the Trail Making Test—Part B, but completion time improved with time (p = .001, ES = −0.40). In conclusion, 3 hr of prolonged sitting decreases Q_{Brain} and executive function independent of glycemic index in young, healthy adults.

KEYWORDS

Doppler ultrasound, executive function, glycemic index, sedentary, total brain blood flow

1 | INTRODUCTION

Chronic sedentary behavior, particularly prolonged sitting, is associated with cognitive impairment and neurodegenerative diseases (Hamer & Stamatakis, 2014; Vancampfort et al., 2018). However, the mechanism(s) linking repeated acute exposure to prolonged (>30 min) sitting have not been determined. One viable pathway is disrupted brain blood flow (Stoner et al., 2019; Wheeler et al., 2017). Though total brain blood flow (Q_{Brain}) may be important, it should be acknowledged that people engage in additional behaviors while sitting, including consuming meals. Of concern, Western meals frequently include highly refined sugar, raising the glycemic index (GI): the value given to foods based on how the affect blood glucose levels (Cordain et al., 2005). This study investigates whether the of prolonged sitting on Q_{Brain}.

For the brain to function properly, it needs continuous blood flow to ensure adequate oxygen and glucose delivery (Marshall, 2001; Wheeler et al., 2017). Regulation of Q_{Brain} is dependent upon sufficient venous return, cerebral autoregulation to maintain perfusion pressures (Willie et al., 2014), and microcirculatory recruitment to maintain perfusion (Attwell et al., 2010; Willie et al., 2014). Prolonged sitting can lead to blood pooling in the lower extremities, decreased venous return, and disruption to Q_{Brain} (Credeur, Miller, et al., 2019; Stoner et al., 2019). While Q_{Brain} was not specifically measured in the limited available literature, it does indicate that prolonged sitting decreases middle cerebral artery blood flow velocity (MCAv) by 5% (Carter et al., 2018; Perdomo et al., 2019). Additionally, the lack of skeletal muscle activity while sitting

also diminishes glucose uptake from the blood, which can trigger oxidative stress, elevate inflammatory cytokines, reduce nitric oxide bioavailability, and induce endothelial dysfunction (Hamilton, 2018). The effects of prolonged sitting on blood glucose are exacerbated following a HGI meal; an exaggerated insulin response and increased glucose variability may downregulate glucose transport in the brain and disrupt vital energy supply (Wheeler et al., 2017).

Disrupted Q_{Brain} and brain vital energy supply may lead to a reduction in executive function (Stamatakis et al., 2011). The term executive function refers to general purpose cognitive processes that are regulated by the prefrontal cortex, and are critical to everyday functioning, human behavior, and the articulation of thoughts (Miyake & Friedman, 2012). The literature investigating uninterrupted prolonged sitting and executive function is mixed; Baker et al. reported that prolonged sitting increases problem solving errors by 56% (Baker et al., 2018), whereas Stoner et al., reported no changes in Stroop Inference Test following 3 hr of sitting (Stoner et al., 2019). However, no previous studies have simultaneously investigated the effects of prolonged sitting on Q_{Brain}, cerebral perfusion, and executive function, and whether an HGI meal exacerbates these effects. Therefore, the primary aim of this study was to determine whether uninterrupted prolonged sitting (3 hr) combined with a HGI meal leads to greater attenuation of Q_{Brain} when compared to prolonged sitting combined with a control (low-glycemic index, LGI) meal.

2 | METHODOLOGY

This study is reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines (Schulz et al., 2018). Ethical approval was obtained from the University of North Carolina at Chapel Hill institutional review board, and all participants were provided written informed consent prior to participating in the study.

2.1 | Participants

Considering limited evidence on the interaction between prolonged sitting and HGI foods, a group of young, healthy adults were selected for this preliminary study to minimize the confounding influence of age and cardiometabolic abnormalities. Twenty young (18–35y), physically active and healthy men and women were recruited from the population of a large state university. The university broadly represents the young population of the state. Exclusion criteria included pregnancy, current smoker, any known cardio-metabolic disorders, or use of medications known to affect cardiovascular function. In women, because fluctuations in

estrogen can affect cardiovascular measures, the first testing session was performed within the first 1–7 days of the onset of their menstrual cycle, and the second condition was performed within 7 days of the previous visit. Women reporting contraceptive use were tested during the placebo week.

2.2 | Experimental design

This study was a double-blind randomized cross-over design with two counterbalanced arms: prolonged sitting following an LGI meal, and prolonged sitting following consumption of an HGI meal. A minimum of 2 days separated visits to minimize carry-over effects, with a maximum of 7 days to minimize within-subject variation. Three hours of sitting was chosen based on prior sitting studies (Bailey et al., 2017; Morishima et al., 2016; Padilla & Fadel, 2017; Stoner et al., 2019), and the fact that peak postprandial glucose concentration time is estimated to be 2 hr post-meal consumption (Ciok & Dolna, 2006). The primary outcome was Q_{Brain}. This was assessed pre-and post-prolonged sitting for each condition. Brain fog was measured during the sitting bouts. A familiarization session preceded the experimental conditions.

2.2.1 | Familiarization

Participants reported to the laboratory to review documentation, provide informed consent and were familiarized with assessments of executive function and all testing equipment. After obtaining height and weight, participants were positioned on a three-section table (Armedica AM353 Hi-Lo, Tiger Medical, Irvington, NJ). The table head section can be repositioned upward 78° and the foot piece downward 90°, enabling passive maneuvering from the fully supine to seated position. In the supine position, the continuous glucose monitor (CGM) (iPro2, Medtronic, Northridge, CA) was inserted into the subject's abdomen, approximately 5 cm lateral to the umbilicus. The CGM was inserted at least 12 hr before the start of each experimental testing visit. An accelerometer (ActiSleep +; ActiGraph LLC, Fort Walton Beach, FL) was also placed on the ankle to covary for spontaneous movement during each study condition as well as to ensure participants refrained from exercise 24 hr prior to the experimental day. A sleep diary and a 24 hr food diary were given to each participant to record their dietary intake the day before each experimental visit. To control for pre-experimental dietary intake, an identical standardized dinner (Lean Cuisine) was consumed the night before each testing day, at least 12 hr before the start of testing, and text messages were sent to ensure participants ate the meal at the same time before each experimental visit.

2.2.2 | Experimental visits

Participants arrived at the laboratory (22 ± 2°C, 26 ± 8.94% humidity) between 06:00 and 10:00 a.m. Participants were fasted and refrained from caffeine intake for at least 12 hr. Additionally, participants were asked to avoid vigorous physical activity and alcohol for 24 hr prior to experimentation. Upon arrival, participants were asked to empty their bladder and then fasting blood glucose concentrations were measured using the CGM. During a 3 hr sitting protocol, blood volume could change throughout due to blood filtration in the kidneys and water loss through perspiration and respiration. To replace predicted water loss, 500 ml of water was provided for participants to consume ad libitum. There were no instances of participants getting up to use the restroom at any point during the study.

Participants were fitted with near infrared spectroscopy (NIRS, PortaLite, Artinis Medical Systems, Netherlands) optodes on the calf and forehead (prefrontal cortex) for the assessment of blood pooling and cerebral perfusion, respectively. Additionally, participants were equipped with a lead II electrocardiogram to measure heart rate (HR), finger photo-plethysmography for the continuous assessment of blood pressure (non-invasive blood pressure [NIBP], ADInstruments, Colorado Springs, CO), and a blood pressure cuff on the left arm for the assessment of central blood pressures via pulse wave analysis (SphygmoCor XCEL, Gold Coast, Queensland, Australia). Following 20 min of quiet rest in the supine position, the participants were read standardized executive function assessment instructions and asked to assess their brain fog, then they performed three 20 s Stroop Inference test measurements, followed by three trials of the Trail Making Test—Part B. The measures of executive function were conducted in the supine position to ensure there was no confounding with the vascular measurements. Following assessments of baseline (supine) perfusion, hemodynamic, and executive function, the participants were passively maneuvered to the seated position. The HGI (glucose; GI: 100) or LGI (fructose; GI: 19) meal (solution in g/kg of participant weight mixed with 300 ml of water, lemon juice given as option to add to make solution palatable) was then administered and participants were given 10 min to drink it. Following meal consumption, participants were instructed to remain seated for 3 hr while watching a non-stimulatory television program to maintain wakefulness. The television program was the same for each participant between visits. Participants were also asked to not fidget. The ankle accelerometer was used to record leg movement (fidgeting) throughout. At 3 hr, participants were passively returned to the supine position and assessments of executive function were repeated for secondary outcome measurements (Figure 1).

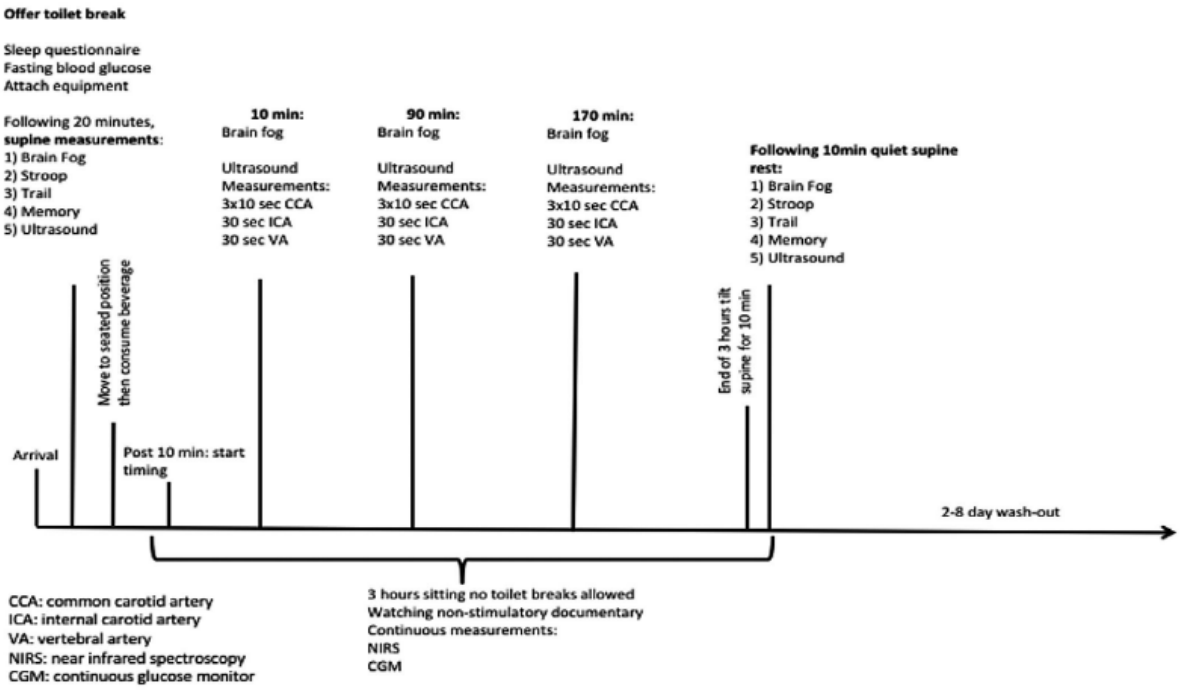

Figure 1 Experimental protocol for HGI and LGI.

2.3 | Experimental measures

2.3.1 | Stimulus: Blood glucose and venous pooling

To confirm the effects of the LGI and HGI meals on glycemia, a CGM (iPro2, Medtronic, Northridge, CA) was used to take glucose readings every 5 min (Service, 2013) across each 3 hr sitting condition. The area under the curve (AUC) was calculated using the trapezoidal rule method, and mean blood glucose (MBG) by averaging the glucose concentrations. The J-index was used as a measure of glucose variability, calculated as $0.324 \times (\text{MBG} + SD)^2$, where *SD* is the standard deviation of glucose concentrations.

Venous pooling in the calf was monitored using a continuous-wave NIRS device (PortaLite, Artinis Medical Systems BV) placed on the medial gastrocnemius. The location of the NIRS device was standardized using a template to aid probe placement, measuring the distance from landmarks, and then taking a picture. Additionally, for the calf measures we used ultrasound to ensure the probe was placed on the fattest portion of the muscle while ensuring blood vessels are avoided. Specifically, deoxygenated hemoglobin (HHb) was used to reflect the concentration of hemoglobin (Hb) in the venous compartment (Jones et al., 2016). The PortaLite is comprised of a single wireless optode consisting of three light emitting diodes, positioned at 30 mm, 35 mm, and 40 mm from a single receiver, which transmitted infrared light at two wavelengths (760 nm and 850 nm). In order to determine absolute Hb concentrations, the PortaLite employs spatially resolved spectroscopy. Spatially resolved spectroscopy is the spatial profile of the intensity of backscattered light measured as a function

of the distance from the light transmitter, with the shape of this function being related to the absorption coefficient, from which absolute oxygenated Hb [HbO2] and HHb concentrations can be measured. A differential path-length factor of 4.0 was used to correct for photon scattering within the tissue, and data were collected at 10 Hz (Oxysoft, Artinis Medical Systems BV). Absolute Hb assessments using this device have been validated against frequency-domain NIRS, and can reliably track orthostatic changes (ICC: 0.72–0.75) (Stone et al., 2016). For each time point data were averaged over 30 s.

2.3.2 | Primary outcome: Brain blood flow and perfusion

A duplex Doppler ultrasound (Logiq P6; GE Medical systems,WI) was used to monitor blood flow through the internal carotid (ICA), vertebral (VA), and common carotid arteries (CCA). The CCA travels superiorly and bifurcates in the neck. The ICA and VA both directly perfuse the Circle of Willis and account for blood flow solely to the cerebral hemispheres, not the face and scalp. The CCA was measured 1.0–2.0cm distal to the carotid bifurcation with their head tilted at 45° (angled to the left), the left ICA 2.0–4.0cm proximal to carotid bifurcation with the chin slightly elevated, and the VA between the transverse processes of the C3 and subclavian artery. The insonation angle was kept constant between 45° and 60° and the sample volume encompassed the entire vessel lumen without extending beyond the near and far walls. At the CCA, 10 s videos were captured (AV. ioHDFrameGrabber; Epiphan Video, Palo Alto, California, USA), during which participants were asked to briefly cease breathing to avoid any artifact due to respiratory movement. At the ICA and VA, 30 s videos were recorded while the participants breathed normally and then broken down into three 10 s videos. The captured videos were analyzed using automated edge detecting software (FMD Studio, Quipu, Italy). Custom written Excel Visual Basic code was used to fit peaks and troughs to the diameter waveforms to calculate diastolic, systolic, and mean diameters, and to automate calculation of study outputs (Bell et al., 2017; Stoner & Mccully, 2012; Stoner & Sabatier, 2012).

Blood flow was calculated from continuous diameter and mean blood velocity recordings using the following equation: $3.14 \times (\text{radius})^2 \times$ mean blood velocity $\times 60$. Q_{Brain} was calculated as [(ICA blood flow + VA blood flow) × 2 (ml/min)] and total head blood flow (Q_{Head}) as [(CCA blood flow + VA blood flow) × 2 (ml/min)] (Sato et al., 2011). The distribution of cardiac output (CO) to the brain and head was calculated as Q_{Brain} /CO × 100 (%) and (Q_{Head})/CO × 100 (%), respectively. The relative contribution of internal carotid blood flow (QICA) and vertebral artery blood flow (QVA) was estimated as QICA/ Q_{Brain} × 100 (%) and QVA/ Q_{Brain} × 100 (%), respectively. Cerebrovascular conductance was calculated as the ratio of Q_{Head}, QICA, and QVA to mean arterial pressure (MAP). Additionally, shear rate (s−1) was calculated as 4×

mean velocity/diameter, and oscillatory index (OI) was calculated from retrograde shear rate/(antegrade shear rate + retrograde shear) × 100 (Credeur et al., 2019).

The prefrontal cortex was assessed due to the key role it plays in executive function since it has the capacity to send top-down signals to cortices to control the information retrieval necessary to complete both the Stroop Inference test and the Trail Making Test—Part B. Prefrontal cortex cerebral perfusion was monitored using the NIRS device. Depending on individual head geometry, the probe was positioned over the participant's prefrontal cortex at Fp1 for right-side dominant participants, and at Fp2 for left-side dominant participants according to the International 10–20 system of electrode placement (Albinet et al., 2014). The outcomes of interest were total hemoglobin (tHb), as a measure of perfusion, and tissue saturation index (TSI%), as a measure of oxygenated blood. The tHb was calculated with manufacturer software using a spatially resolved spectroscopy approach. For each time point data were averaged over 30 s.

2.3.3 | Secondary outcome: Executive function, memory, and brain fog

Executive function was assessed using the Stroop Inference Test and the Trail Making Test—Part B. The Stroop and the Trail Making Test (TMT) were administered prior to and following each 3 hr sitting bout. The Stroop Inference test (Xavier Educational Software Ltd., Bangor, UK) is a classic measure of prefrontal cortex function (MacLeod, 1991) that has been widely used to assess cognition (Faulkner et al., 2016, 2017; Lambrick et al., 2016; Lucas et al., 2012; Stoner et al., 2019). The Stroop Inference test involves four words (blue, yellow, green, and red) being randomly presented, consecutively. The color that each word is presented in is either congruent or incongruent with the relevant semantic information (e.g., blue presented in the color blue or the color green). For this task, 20 s was allotted for each of the three trials and averaged. The response time, total number of correct, and percentage correct were recorded. Acceptable reliability has been reported for both word (ICC: 0.71) and color (IC: 0.79) tasks in young adults (Strauss et al., 2005).

The TMT—Part B has been used in prior studies as an assessment of executive function in young, healthy populations (Falck et al., 2017). The TMT—Part B presents numbers and letters placed in a semi-random fixed order, in such a manner to avoid overlapping lines being drawn. The participant connected 25 encircled numbers and letters in numerical and alphabetical order, alternating between the numbers and letters. For example, the first number "1" is followed by the first letter "A," followed by the second number "2" then second letter "B," and so on (Bowie & Harvey, 2006). Time to completion was recorded, and the test was

repeated three times then averaged. Accepted reliability (ICC: 0.85) has been reported for the TMT—Part B in healthy adults ranging from 18 to 84 years old (Woods et al., 2015).

Memory recall was assessed using the word list component of the Hopkins Verbal Learning Test (Grenfell-Essam et al., 2018). Participants read word lists from the Hopkins Verbal Learning Test at the rate of one word every 2 s in a supine position prior to 3 hr of sitting. The Hopkins Verbal Learning test word lists contain 12 words, 4 words from 3 semantic categories. After 3 hr of sitting, participants were moved to a supine position and asked to recall any of the words during the posttest. The participants verbally confirmed that they understood the aim and meaning of the memory recall test prior to 3 hr of sitting.

Previous studies have reported prolonged sitting to increase sleepiness, mental effort, and mental fatigue (Perdomo et al., 2019; Wennberg et al., 2016). To encapsulate sleepiness and mental effort/fatigue in a simple scale, we modified the Borg Category scale with Ratio properties (CR10) scale to assess “Brain fog”: subjectively defined as exaggerated mental fatigue (Ocon, 2013). This scale is a self-report of level of fogginess and has a 10-point Likert scale from 0 “not foggy –very focused” to 10 “maximal fogginess –cannot focus.” This is not a standard assessment, thus data collected were deemed exploratory.

2.3.4 | Mechanistic outcome: Hemodynamics and arterial stiffness

Heart rate was measured using a Lead II electrocardiogram (Powerlab Bioamp, ADInstruments, Colorado Springs, CO). Blood pressure was measured using a dual-cuff finger photoplethysmography system (non-invasive blood pressure [NIBP], ADInstruments, Colorado Springs, CO). The finger cuffs were placed on the middle-and index fingers of the right hand, and a height correction system to the level of the right atrium on the midaxillary line. Data were sampled at 1,000 Hz using the Powerlab data acquisition device (30 series, ADInstruments, CO). Stroke volume (SV) was estimated using the Model flow method (Wesseling et al., 1993), CO as SV X HR, and systemic vascular conductance (SVC) as CO/MAP.

Local pulse wave velocity (PWV) was measured in the ICA, VA, and CCA arteries to determine whether arterial stiffening occurred under the experimental conditions. A brightness mode ultrasound (Logiq P6) device equipped with a 12 MHz linear array probe was used to collect arterial diameters over the cardiac cycle (30 Hz), and central blood pressures were measured using pulse wave analysis (SphygmoCor XCEL, Gold Coast, Queensland, Australia). PWV

was calculated using the equation: PWV = sqrt ((β × diastolic blood pressure [DBP]) / (2*p*)), where β is the is the β stiffness index, and *p* is the assumed blood density (1,059 kg/ m^3) (Harada et al., 2002).

2.4 | Randomization

This study was a double-blind study. Randomization was performed by chance, where 2 sets of 10 unique numbers were generated from a number range of 1–20 (www.randomizer.org). Solutions were masked and assigned at "A and B." The randomization procedure and solution assignment were performed by an uninvolved research assistant. Both the participants and researchers assessing outcomes were blinded to interventions. Solutions were unmasked following statistical analyses.

2.5 | Sample size

To estimate the sample size required to detect the smallest detrimental (or beneficial) effect in a cross-over study (Hopkins et al., 2009) with a Type I error rate of 0.05 and 80% power, approximately 18 participants were required to detect a small effect change (ES: 0.2) in Q_{Brain}. Twenty participants were recruited for the experimental protocol to account for potential missing data.

2.6 | Statistical analysis

Statistical analyses were performed using the RKWard (version 0.7.1), a front end to the R programming language. Only participants who had complete data for the primary outcomes were included in the analyses. Raw data are presented as mean [*SD*] and mixed model data are presented as mean [95% confidence interval (95%CI)]. The corresponding author had full access to the data in the study and was responsible for the integrity of the data set and the data analyses. The α level was set a priori for all statistical procedures at α = 0.05.

The Hopkins Verbal Learning Test (memory test), glucose AUC, physical activity, and sleep were analyzed using the Student's paired *t* test. For all other data, the effects of time and sitting condition were analyzed using linear mixed models, with random effects of subject (intercept) and fixed effects of time (slope) and condition. To limit within-subject variance, the models were adjusted for baseline values (Kenward & Roger, 2010). To account for correlated error variances, that is, repeated measures for each participant, mixed effects regression was used to estimate the relationship between the glucose variables and the measures of brain blood flow and perfusion, with random effects of subject (intercept) and fixed effects of the

covariate (glucose outcome) (Service, 2013). Effect sizes (ES) were calculated as Cohen's *d*, where ≤0.2, 0.2, 0.5, and 0.8 were defined as trivial, small, moderate, and large. For the mixed models Cohen's *d* was calculated as the effect β divided by *SD*.

3 | RESULTS

3.1 | Participants

Twenty participants were recruited, of which 18 (22.6 [*SD*: 3.1] y, 33% F, 24.3 [*SD*: 3.7] kg/m^2) completed both study conditions and self-identified as non-Hispanic White (*n* = 13), African American (*n* = 2), and Middle-eastern (*n* = 3). There were two participants who dropped out due to illness (*n* = 1) and time commitments (*n* = 1). All female participants were on some type of birth control. The number of data points available for each outcome is listed in the tables.

3.2 | Control data

The night before data collection, the total minutes in bed averaged 304.7 [*SD*: 25.1] min for the HGI condition and 433.3 [*SD*:53.5] for the LGI condition (*p* = .423). There was no significant difference between total moderate-vigorous physical activity during the 24 hr prior to experimental visits (HGI: 42.2 [*SD*: 33.5], LGI: 52.4 [*SD*: 40.8] minutes, *p* = .079). Additionally, the AUC for blood glucose data12 hr prior to experimental visits was similar between LGI and HGI (64,330 [*SD*: 19.9] and 65,936 [*SD*: 14.3], respectively, *p* < .05).

3.3 | Stimulus data

Figure 2 illustrates the average blood glucose (mg/dl) across both conditions. The AUC was significantly greater for HGI compared to LGI (*p* = .005, ES = 0.90), as was MBG (*p* = .004, ES = 0.93) and J-index (<0.001, ES = 1.29). The raw data and mixed model findings for medial gastrocnemius HHb (venous pooling) are presented in Table 1. The interaction effect trended significant (*p* = .073), with HHb increasing 18.7% for HGI (4.25 μM, 95%CI: 0.87 to 7.52, ES = 0.29) and not significantly changing for LGI (−0.17 μM, 95%CI: −3.48 to 3.14).

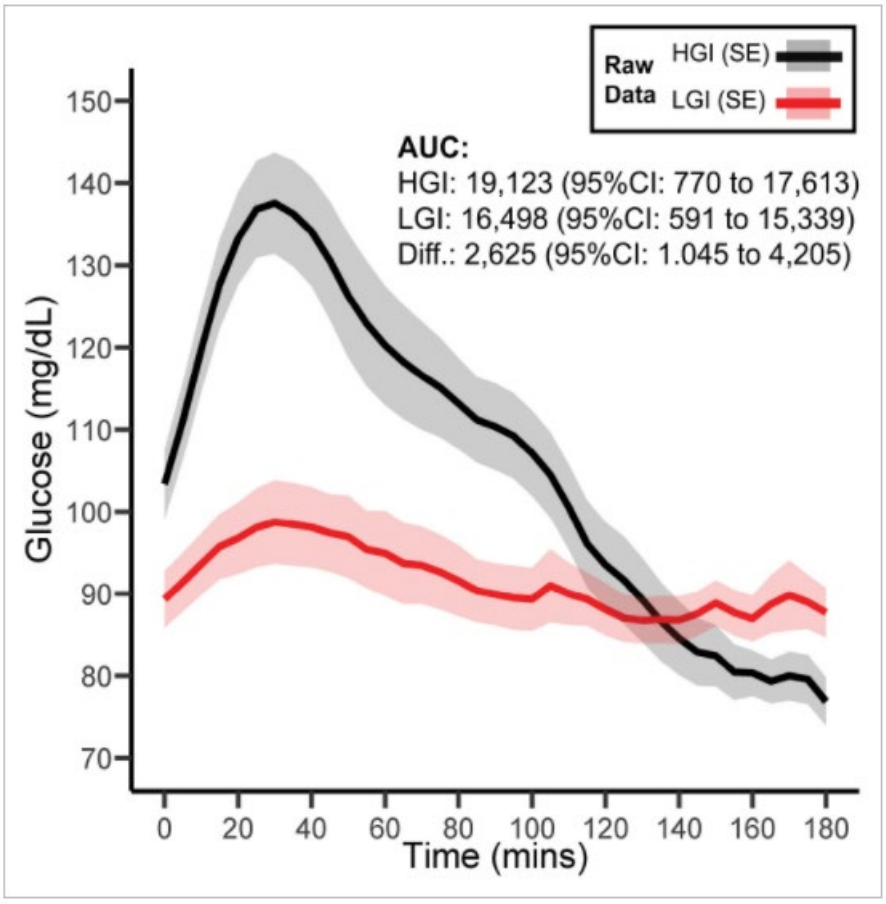

Figure 2 Average blood glucose (mg/dl) responses across prolonged (3 hr) sitting following a high- or low-GI meal. (n = 18 for outcome). HGI, high-glycemic index meal; LGI, low-glycemic index meal.

3.4 | Primary outcome: Brain blood flow and perfusion

The adjusted mixed model Q_{Brain} data are presented in Figure 3, and the raw data for Q_{Brain} and the individual blood vessels are presented in Table 2. Table S1 in the supplement reports the associations between measures of brain blood flow and glucose outcomes. There were nonsignificant interaction (p = .216) and condition effects (p = .174) for Q_{Brain}, though the time effect was significant (p = .001, ES = −0.26). Q_{Brain} decreased across both sitting conditions, and this change was driven by Q_{ICA} (p = .003, ES = −0.36) which significantly decreased by 14.7% (−74.0 ml/min, 95%CI: −121 to −26.7) across both sitting conditions, whereas Q_{VA} did not (p = .942, ES = −0.01). There were nonsignificant effects on the distribution of blood through the ICA and VA, and the proportion of CO delivered to the brain. Similarly, there were nonsignificant effects on cerebral perfusion.

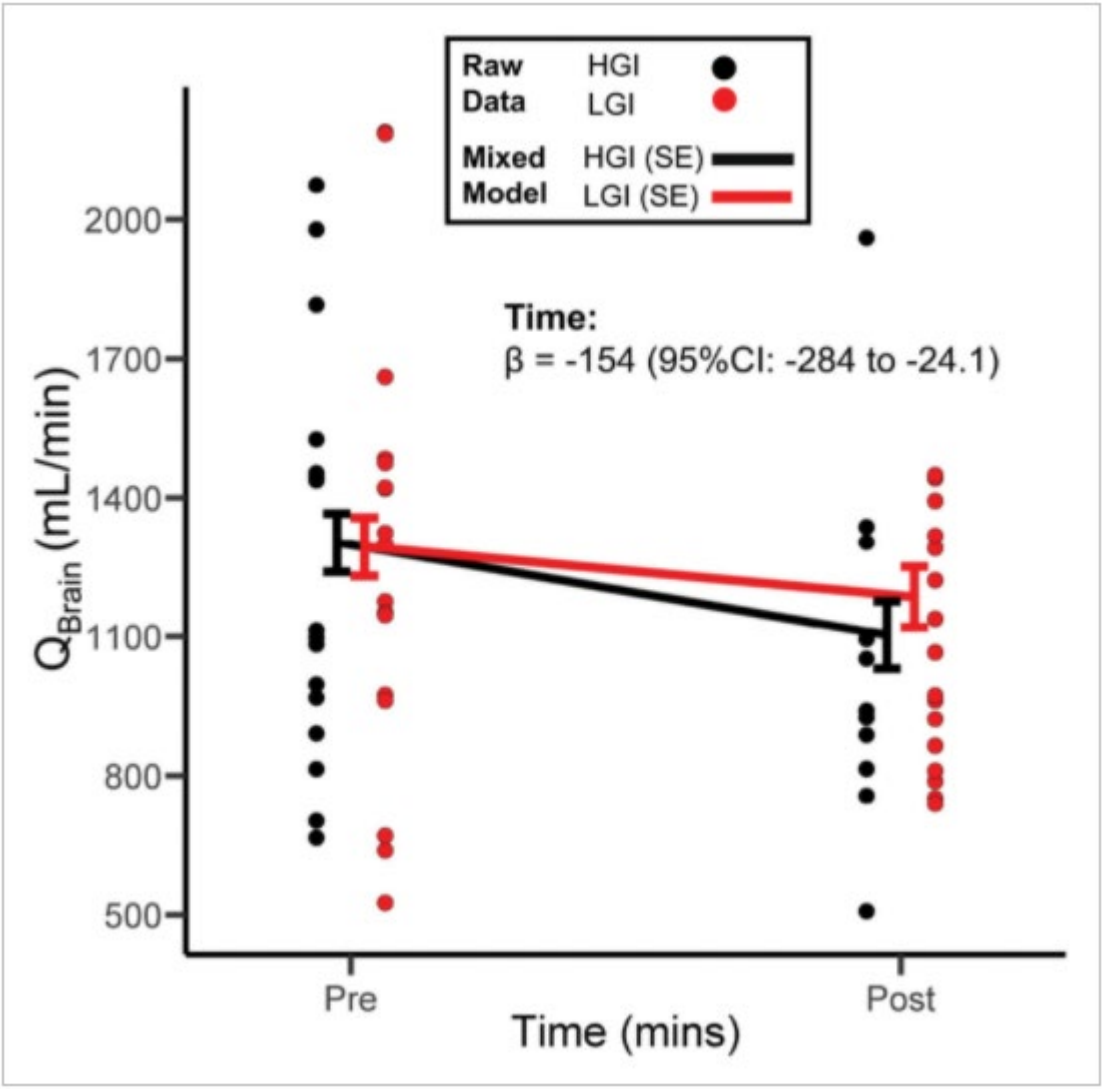

Figure 3 Pre versus Post (supine) total brain blood flow responses. (n = 18 for outcome). HGI, high-glycemic index meal; LGI, low-glycemic index meal; QBrain, total brain blood flow.

MBG was significantly associated with a decrease in Q_{ICA} (β = −2.99 ml/min, 95%CI: −5.77 to −0.21, p = .043, ES = −0.42), though the J-index was not significantly associated (β = −6.27 ml/min, 95%CI: −14.3 to 1.77, p = .136, ES = −0.52). Neither MBG (p = .776, ES: −0.12) nor J-index (p = .819, ES: −0.16) was significantly associated with Q_{Brain} or perfusion outcomes.

Table 1 Supine Hemodynamic, conductance, and calf blood pooling responses to prolonged sitting (3 hr) combined with a low-glycemic

		Hemodynamics				Vascular conductance				Pooling
		MAP mm Hg	CO L/min	SV ml	HR bpm	SVC	ICA ml/min/mm Hg	VA	Brain	HHb µM
Data points		**72/72**	**70/72**	**70/72**	**70/72**	**70/72**	**72/72**	**64/72**	**64/72**	**71/72**
Mean averages										
HGI	Pre	79.7	3.56	57.0	61.7	44.8	6.34	1.92	14.9	21.1
	Post	79.3	3.62	57.5	61.7	42.9	5.51	1.95	14.7	25.6
LGI	Pre	79.4	3.50	57.8	60.3	44.1	6.53	1.91	16.8	24.7
	Post	81.4	3.68	58.1	68.3	45.1	5.27	1.96	14.1	24.5
Standard deviations										
HGI	Pre	6.27	1.19	15.4	11.5	14.4	2.44	1.20	6.70	9.80
	Post	6.79	1.00	13.4	11.6	16.3	1.82	1.73	6.17	10.0
LGI	Pre	7.32	0.86	8.7	12.0	10.0	3.07	0.93	6.88	9.29
	Post	6.90	0.92	17.4	16.5	10.5	2.81	1.11	6.70	8.98
Interaction effect										
	β	2.37	0.13	-0.33	7.98	0.04	-0.63	-0.06	-1.78	-4.42
	P	0.124	0.718	0.950	0.054	0.964	0.306	0.903	0.301	0.073
	ES	0.18	0.04	-0.01	0.24	0.01	-0.12	-0.02	-1.31	-0.22
Time effect										
	β	0.78	0.12	0.40	4.03	0.58	-0.95	-0.05	-2.12	2.04
	P	0.309	0.504	0.881	0.052	0.515	0.003	0.820	0.016	0.097
	ES	0.12	0.08	0.02	0.24	0.08	-0.37	-0.03	-0.31	0.20
Condition effect										
	β	1.15	0.06	0.09	3.70	0.15	-0.24	-0.10	-0.74	-1.56
	P	1.35	0.74	0.974	0.075	0.89	0.435	0.667	0.391	0.211
	ES	0.18	0.04	0.00	0.11	0.02	-0.09	-0.05	-0.11	-0.15

3.5 | Secondary outcome: Cognition

Cognitive outcomes are reported in Table 3 and the brain fog data during sitting are shown in Figure 4. There were nonsignificant interaction (p = .107) and condition effects (p = .445) for Stroop reaction time, though the time effect was significant (p = .024, ES = 0.27). Across conditions, reaction time increased (got worse) by 4.8% (0.04 ms, 95%CI: 0.01 to 0.08). Similarly, there were nonsignificant interaction (p = .327) and condition effects (p = .612) for brain fog during sitting (Table 3), but across time brain fog increased by 33.3% (p = .025, ES =0.35). For the Hopkins Verbal Learning Test, there was a nonsignificant condition effect (p = .375, ES: −0.12). For the TMT—Part B, there were nonsignificant interaction (p = .772) and condition effects (p = .729), but there was a significant time effect (p = .001, ES = −0.40). Across time, completion time decreased (improved) by 10.6% (−12.64 s, 95%I: −4.16 to −1.12).

Table 2 Supine Brain blood flow and perfusion responses to prolonged sitting (3 hr) combined with a low-glycemic index (LGI) or high-glycemic index (HGI) meal

		Brain Blood Flow				Distribution		% Cardiac Output		Perfusion	
		Q_{CCA}	I_{CA}	V_A	Q_{Brain}	ICA	VA	Q_{Brain}	Q_{Head}	tHb	TSI
		ml/min				%		%		µM	%
Data points		**72/72**	**72/72**	**64.72**	**64.72**	**64/72**	**64/72**	**62/72**	**62/72**	**71/72**	**71/72**
Mean averages											
HGI	Pre	723	489	156	1762	75.6	24.4	39.2	53.7	65.4	57.2
	Post	540	435	154	1384	75.1	24.9	37.4	43.8	68.7	59.7
LGI	Pre	737	517	150	1795	75.3	24.7	42.1	56.1	69.5	60.9
	Post	623	424	157	1582	71.3	28.7	35.7	50.6	66.7	60.9
Standard deviations											
HGI	Pre	185	174	103	459	10.7	10.7	19.3	22.6	18.0	7.6
	Post	155	142	132	514	12.7	12.7	29.5	32.4	24.7	5.9
LGI	Pre	180	241	72	434	12.4	12.4	21.7	21.9	19.7	7.3
	Post	206	222	89	550	12.9	12.9	21.8	27.0	19.5	8.0
Interaction effect											
	β	69.9	-39.5	12.5	211	-0.42	4.42	-4.83	-8.41	0.57	1.28
	P	0.216	0.416	0.751	0.156	0.285	0.285	0.473	0.500	0.239	0.121
	ES	0.06	-0.10	0.04	0.18	-0.01	0.13	-0.09	0.09	-0.14	-0.19
Time effect											
	β	-149	-74.0	-1.43	-304.0	-1.78	1.78	-4.63	-8.41	0.57	1.28
	P	<0.001	0.003	0.942	<0.001	0.389	0.389	0.173	0.064	0.840	0.127
	ES	-0.26	-0.36	-0.01	-0.52	-0.11	0.11	-0.18	-0.24	0.02	0.18
Condition effect											
	β	38.5	-14.2	4.67	111	-2.26	2.26	-2.09	3.33	-2.85	0.68
	P	0.174	0.559	0.812	0.137	0.274	0.274	0.537	0.458	0.315	-0.676
	ES	0.07	-0.08	0.03	0.19	-0.14	0.14	-0.07	0.10	-0.12	-0.09

Abbreviations: CO, cardiac output; ES, effect size; HHb deoxygenated hemoglobin (calf blood pooling); HR, heart rate; QBrain, total brain blood flow; QCCA, common carotid artery blood flow; QHead, total head blood flow; QICA, internal carotid artery blood flow; QVA, vertebral artery blood flow; SD, standard deviation; SV, stroke volume; tHb, total hemoglobin (prefrontal cortex); TSI, tissue saturation index (prefrontal cortex).

3.6 | Mechanistic data

Hemodynamic and vascular conductance data are presented in Table 1. The effects were non-significant for MAP, CO, and SV. The interaction effect for HR trended significant (p = .052). For LGI, HR increased 13.1% (8.01 beats per minute [bpm], 95%CI: 2.35 to 13.9), while there was no change for HGI (0.04 bpm, 95%CI: −0.58 to 5.88). The effects were non-significant for SVC and VA conductance. However, there were significant interaction effects for ICA (p = .003) and brain conductance (p = .016). ICA conductance decreased 15.1% (−0.95 ml min^{-1} mm^{-1} Hg, 95%CI: −1.55 to −0.36), and brain conductance decreased 13.0% (−0.74 ml min^{-1} mm^{-1} Hg, 95%CI: −3.79 to −0.45).

Table 3 Cognitive responses to prolonged sitting (3 hr) combined with a low-glycemic index (LGI) or high-glycemic index (HGI) meal

		Stroop			Trail	Fog	Memory
		RT	Correct	Accuracy	Time	Score	Correct
		ms	#	%	ms	x/9	#
Data points		**72/72**	**72/72**	**72/72**	**72/72**	**72/72**	**36/72**
Mean averages							
HGI	Pre	0.88	16.7	100	25.9	2.44	0.00
	Post	0.94	18.4	100	23.0	3.11	0.47
LGU	Pre	0.94	18.2	100	23.4	2.22	0.00
	Post	0.96	18.8	100	21.0	2.94	0.51
Standard deviations							
HGI	Pre	0.22	4.28	0.98	8.62	1.54	0.00
	Post	0.22	4.14	0.00	6.91	2.05	0.18
LGI	Pre	0.19	3.72	1.12	7.66	1.17	0.00
	Post	0.17	3.15	1.01	5.57	2.26	0.18
Interaction effect							
	β	-0.04	-1.17	-0.31	0.45	0.06	
	P	0.249	0.107	0.386	0.772	0.928	
	ES	-0.14	-0.19	-0.10	0.03	0.01	
Time effect							
	β	0.04	1.17	0.18	-2.64	0.69	
	P	0.024	0.0002	0.322	0.001	0.027	
	ES	0.27	0.39	0.12	-0.40	0.27	
Condition effect							
	β	-0.01	-0.38	-0.12	-0.27	-0.03	-0.02
	P	0.445	0.303	0.502	0.729	0.926	0.37
	ES	-0.09	-0.12	-0.09	-0.04	-0.01	-0.12

Abbreviations: ES, effect size; RT, reaction time; SD, standard deviation.

3.7 | Ancillary analysis

Additional data, including OI and PWV, are reported in supplemental Table S2. The effects were non-significant for all outcomes.

4 | DISCUSSION

The major findings of this study are that Q_{Brain}, Stroop Inference Test scores, and brain fog were impaired with prolonged sitting. However, prefrontal cortex cerebral perfusion did not change with prolonged sitting, and contrary to expected, TMT—Part B improved with time. Meal type (HGI vs LGI) did not significantly affect any of the outcomes.

4.1 | Limitations and strengths

To better contextualize the discussion, the limitations and strengths of the current study must be stated. First, we purposefully elected to recruit a group of healthy, active, young adults to

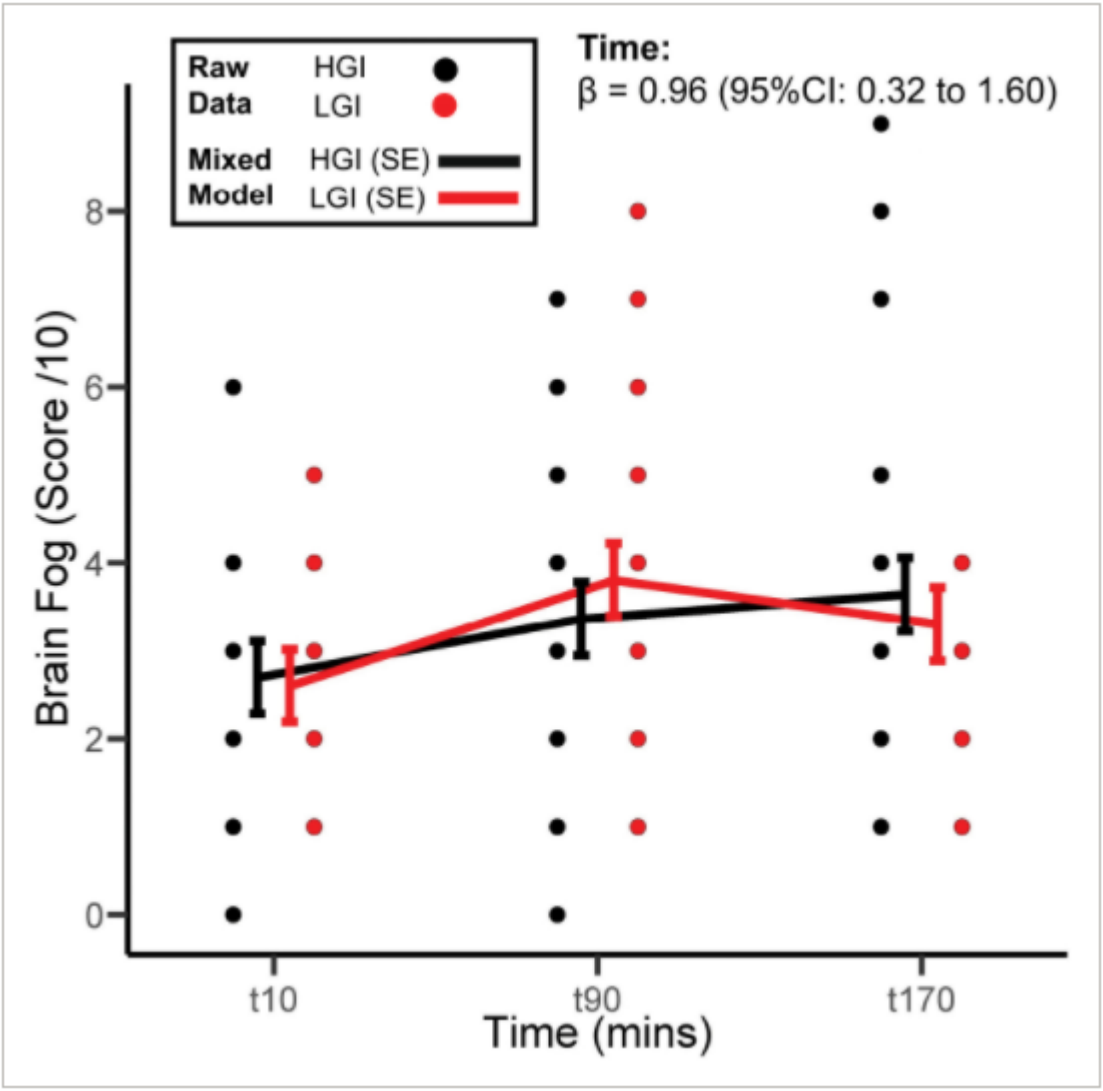

Figure 4 Seated brain fog responses across prolonged (3 hr) sitting. (n = 18 for outcome). HGI, high-glycemic index meal; LGI, low-glycemic index meal.

minimize the confounding influence of age and cardiometabolic diseases. Future studies are warranted to determine whether the findings are generalizable to other populations. Second, while we did recruit young, healthy participants, the health history screening questionnaire did not ask questions pertaining to cognitive disorders. As such, we cannot discount that the presence or absence of cognitive disorders confounded the findings. Another limitation to consider is that only the TMT— Part B was used, whereas if it were combined with the TMT— Part A, which is known to assess processing speed, a more concrete executive function score may have been achieved. Lastly, we were not adequately powered to examine sex differences in our hypotheses; however, the experimental session did take place at the same stage of the subject's menstrual cycle. Although this study has a few limitations, it also has several strengths including a novel perspective on how consumption of an HGI meal affects Q_{Brain}

during prolonged sitting, which helps to expand the knowledge on the cerebrovascular effects of prolonged sitting.

4.2 | Comparison to literature

4.2.1 | Brain blood flow

The primary aim of this study was to determine whether prolonged sitting (3 hr) combined with an HGI meal disrupts both Q_{Brain} and perfusion to the area of the brain used for executive function. This study found that Q_{Brain} decreased with prolonged sitting, irrespective of meal type. Our belief was that prolonged exposure to hyperglycemia and subsequent hypoglycemia, that is, glycemic variability, would disrupt Q_{Brain}. This belief was based on previous studies reporting that the glycemic variables are associated with impaired macrovasculature and microvasculature function (Geraldes et al., 2009; Joy et al., 2015). However, these aforementioned studies did no investigate the cerebrovascular. For the current study we looked at the association between glycemic variability (estimated using J-index) and Q_{Brain}, but the association was not significant. However, we did see an association between MBG and QICA. It is possible that the young, healthy adults in the current study were able to maintain Q_{Brain} following the consumption of an HGI meal.

There were nonsignificant time and condition effects for prefrontal cortex cerebral perfusion. When interpreting these findings, the vascular anatomy at the base of the brain should be considered. The carotid and vertebrobasilar arteries form a circle of communicating arteries known as the Circle of Willis, and then blood pumped from the heart passes through the common and internal carotid arteries into the circle via the MCA. The MCA supplies a portion of the frontal lobe in the microvasculature which must be recruited to enable prefrontal cortex cerebral perfusion. Considering we found a decrease in Q_{Brain} with prolonged sitting, and that previous studies have reported decreased MCAv (Carter et al., 2018; Perdomo et al., 2019), a decrease in prefrontal cortex cerebral perfusion may also be expected. However, this study and our previous study (Stoner et al., 2019) demonstrated that prefrontal cortex cerebral perfusion does not decrease with prolonged sitting. This indicates that the prefrontal cortex microvasculature may auto-regulate to ensure adequate oxygen delivery (Willie et al., 2014), at least in young, healthy populations.

4.2.2 | Executive function

We hypothesized that prolonged (3 hr) sitting combined with a HGI meal would impair executive function. In line with expectations, we saw a decrease in Q_{Brain}, and as expected,

Stroop performance and brain fog were impaired with prolonged sitting. However, there was no condition effect. Collectively, our current findings, together with those of Perdomo et al. (Perdomo et al., 2019) suggest that prolonged sitting leads to an increase in perceived brain fog, sleepiness, mental effort, and mental fatigue.

Contrary to expected, TMT—Part B times improved across both conditions. These findings align with a previous study in our group (Stoner et al., 2019) that found executive function did not get worse with prolonged sitting. A possible explanation, the TMT—Part B may activate different regions of the prefrontal cortex (Shibuya-Tayoshi et al., 2007) compared to the Stroop Inference test. For example, the Stroop Inferencer Test has consistently been shown to activate a large fronto-parietal network (Grandjean et al., 2012), which is comprised mainly of the anterior cingulate cortex and the dorsolateral prefrontal cortex (DLPC). The DLPC is a region in the frontal lobe that is frequently associated with executive function (Curtis & D'Esposito, 2003). With respect to TMT—Part B, one study reported that the left dorsomedial prefrontal region of the frontal lobe is activated (Miskin et al., 2016). However, this neurophysiological rationale conflicts with the findings from this study, in which perfusion to the prefrontal cortex was maintained. An alternative explanation is that the ordering of the cognitive tests played a role. Specifically, Stroop test was performed prior to the TMT and may have primed the frontal lobe (Race et al., 2009), which would help to explain why Trail time improved across conditions. However, it would be out of the scope of this article to further speculate as more work is needed to fully understand areas of the brain associated with these tests.

5 | IMPLICATIONS AND CONCLUSIONS

While previous studies have associated chronic sedentary behaviour with reductions in brain volume (Siddarth et al., 2018) and cognitive dysfunction (Edwards & Loprinzi, 2017; Hamer & Stamatakis, 2014), less is known about the mechanism(s) linking repeated acute sedentary behavior exposure to chronic cerebrovascular complications. Additionally, there is limited investigation exploring how lifestyle factors, such as dietary choices like HGI meals, may impact these cognitive complications. Findings from this study indicate that Q_{Brain} decreases during prolonged sitting, irrespective of the glycemic index of the meal. Collectively, the findings indicate that while Q_{Brain} decreases with sitting, oxygen delivery to the prefrontal cortex is maintained in healthy, young subjects. The current area of investigation should be repeated in an older population and those with chronic diseases to increase generalizability.

The purpose of this study was to determine whether prolonged sitting (3 hr) combined with an HGI meal leads to greater attenuation of Q_{Brain} when compared to prolonged sitting combined with an LGI meal. We found that prolonged sitting decreased Q_{Brain} across both conditions, and there was a nonsignificant difference between conditions. However, contrary to expected, prefrontal cortex cerebral perfusion did not change with condition or time. Future studies are warranted to measure Q_{Brain}, MCAv, prefrontal cortex cerebral perfusion, and autoregulation simultaneously to help further understand the effects of prolonged sitting on cerebrovascular function.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

SUPPLEMENTARY MATERIAL

TABLE S1 Relationship between glucose variables and change in brain blood flow and perfusion outcomes. β, beta; ES, effect size; LCI, lower confidence interval (95%); MBD, mean blood glucose; QBrain, total brain blood flow; QICA, internal carotid artery blood flow; SD, standard deviation (of blood glucose values); tHb, total hemoglobin (prefrontal cortex); TSI, tissue saturation index (prefrontal cortex); UCI upper confidence interval (95%)

	β	**LCI**	**UCI**	**P**	**ES**
Change in Q_{ICA} (data points = 35)					
MBG	2.99	0.21	5.77	0.043	0.42
SD	1.74	-3.40	6.88	0.510	0.18
J-index	6.27	-1.77	14.3	0.136	0.52
Change in Q_{Brain} (data points = 29)					
MBG	1.79	-10.4	14.0	0.776	0.12
SD	4.26	-18.3	26.8	0.714	0.21
J-index	4.05	-30.3	38.4	0.819	0.16
Change in tHb (data points = 34)					
MBG	0.11	-0.22	0.44	0.404	0.05
SD	0.44	-0.13	1.01	0.140	0.14
J-index	0.68	-0.24	1.60	0.159	0.17
Change in TSI (data points = 34)					
MBG	0.07	-0.03	0.18	0.169	0.05
SD	0.097	-0.08	0.28	0.140	0.05
J-index	0.24	-0.05	0.53	0.109	0.11

TABLE S2 Oscillatory index and pulse wave velocity responses prolonged sitting (3 hours) combined with a low glycemic index (LGI) or high glycemic index (HGI) meal. CCA, common carotid artery; ES, effect size; ICA, internal carotid artery; RT, reaction time; SD, standard deviation; VA, vertebral artery

		Oscillatory Index			**Pulse Wave Velocity**		
		CCA	**ICA**	**VA**	**CCA**	**ICA**	**VA**
		Ratio	**Ratio**	**Ratio**	**m/s**	**m/s**	**m/s**
Data points:		**72/72**	**72/72**	**64/72**	**72/72**	**71/72**	**64/72**
Mean Averages							
HGI	Pre	0.58	3.07	1.92	5.22	5.75	6.43
	Post	1.17	3.67	3.38	4.94	5.71	6.27
LGI	Pre	0.35	1.73	5.77	5.03	5.77	7.43
	Post	0.46	1.88	3.59	5.12	5.45	6.21
Standard Deviations							
HGI	Pre	1.01	4.95	3.42	0.86	1.06	1.67
	Post	1.90	4.48	6.52	0.91	1.34	2.24
LGI	Pre	0.47	2.67	8.49	0.82	1.37	3.53
	Post	0.68	3.09	7.66	0.84	1.44	1.68
Interaction Effect							
	β	-0.48	-0.46	-0.20	0.37	-0.22	-1.21
	P	0.314	0.748	0.350	0.070	0.575	0.135
	ES	-0.12	-0.04	-0.01	0.22	-0.07	-0.19
Time Effect							
	β	0.35	0.37	0.54	-0.09	-0.15	-0.74
	P	0.236	0.714	0.619	0.382	0.447	0.066
	ES	0.18	0.06	0.06	-0.10	-0.09	-0.23
Condition Effect							
	β	-0.32	-0.73	-0.56	0.16	-0.10	-0.28
	P	0.191	0.735	0.620	0.117	0.447	0.494
	ES	-0.16	-0.12	-0.03	0.19	-0.06	-0.09