


**SPECIAL ISSUE TITLE: AGING AND CEREBROVASCULAR HEALTH: STRUCTURAL, FUNCTIONAL, COGNITIVE, AND METHODOLOGICAL IMPLICATIONS****Changes in cerebral perfusion following a 12-month exercise and diet intervention****Chelsea M. Stillman<sup>1</sup>  | John Jakicic<sup>2</sup> | Renee Rogers<sup>2</sup> | Alfonso J. Alfini<sup>3</sup> | J. Carson Smith<sup>4</sup> | Jennifer Watt<sup>1</sup> | Chaeryon Kang<sup>5</sup> | Kirk I. Erickson<sup>1</sup>**<sup>1</sup>Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA<sup>2</sup>Department of Health and Physical Activity, University of Pittsburgh, Pittsburgh, PA, USA<sup>3</sup>Department of Mental Health, Johns Hopkins University, Baltimore, MD, USA<sup>4</sup>Department of Kinesiology, University of Maryland, College Park, MD, USA<sup>5</sup>Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, USA**Correspondence**

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**Funding information**

This research was supported by funding from NIH/NIDDK grants R01HL103646 (PI: Jakicic) and R01DK095172 (PI: Erickson)

**Abstract**

Overweight and obesity may damage the cerebrovascular architecture, resulting in a significant reduction in cerebral blood flow. To date, there have been few randomized clinical trials (RCT) examining whether obesity-related reductions in cerebral blood flow could be modified by weight loss. Further, it is unknown whether the behavioral intervention strategy for weight loss (i.e., diet alone or diet combined with exercise) differentially influences cerebral blood flow in adults with overweight or obesity. The primary aim of this study was to determine whether a 12-month RCT of exercise and diet increases cerebral blood flow in 125 midlife (Mean age  $\pm$  SD = 44.63  $\pm$  8.36 years) adults with overweight and obesity. Further, we evaluated whether weight loss via diet combined with aerobic exercise has an added effect on changes in cerebral blood flow compared to weight loss via diet alone and whether there were regionally specific effects of the type of behavioral intervention on cerebral blood flow patterns. Consistent with our predictions, a 12-month diet and exercise program resulting in 10% weight loss increased cerebral blood flow. These effects were widespread and extended throughout frontal, parietal, and subcortical regions. Further, there was some regional specificity of effects for both diet-only and diet combined with exercise. Our results demonstrate that weight-related reductions in cerebral blood flow can be modified by 10% weight loss over the course of 12 months and that interventions involving exercise exposure may provide unique effects on cerebral blood flow compared to interventions involving only diet.

**KEYWORDS**

arterial spin labeling, blood flow, dosage effects, exercise, obesity, weight loss

**1 | INTRODUCTION**

More than one-third of the U.S. population has obesity (i.e., a body mass index (BMI)  $\geq$  30, kg/m<sup>2</sup>) and approximately 68% of adults in the United States are considered overweight (BMI > 25) (Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016; Ogden,

Lamb, Carroll, & Flegal, 2010). Obesity increases risk for numerous diseases including heart disease, cerebrovascular disease, and Type 2 diabetes mellitus. Notably, these diseases damage the cardiovascular system and disrupt oxygen exchange in the body and in the brain (Giordano, 2005; Grundy et al., 1999; Prasad, Sajja, Naik, & Cucullo, 2014; Stern, 1995).

Obesity has been linked to poorer brain health. For example, individuals with obesity display altered brain activation compared to their healthy weight counterparts, particularly in regions associated with reward processing and executive functioning (Pursey et al., 2014; Stillman, Weinstein, Marsland, Gianaros, & Erickson, 2017). In prospective longitudinal studies, there are increased rates of cortical atrophy (Gustafson, Lissner, Bengtsson, Björkelund, & Skoog, 2004; Ward, Carlsson, Trivedi, Sager, & Johnson, 2005), white matter disease (Gustafson, Steen, & Skoog, 2004), and neurodegenerative disease (e.g., Alzheimer's disease) (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Kivipelto et al., 2005) in populations with overweight and obesity. Importantly, studies have documented negative correlations between BMI and brain glucose metabolism in healthy samples with a BMI range from normal weight to obesity (Volkow et al., 2009), suggesting that brain function may also be compromised in overweight individuals.

Structural and functional brain differences in relation to overweight and obesity may reflect impairments in the cerebrovascular architecture, which is responsible for delivering oxygenated blood and nutrients throughout the brain. For example, there is evidence that overweight and obesity are associated with global reductions in cerebral blood flow (Dorrance, Matin, & Pires, 2014). One mechanism for the observed reductions in cerebral blood flow in obesity may be via blunted cerebrovascular and cardiovascular reactivity—that is, via decreases in arterial carbon dioxide (CO<sub>2</sub>) receptor sensitivity (Phillips, 2011). Although it is not yet fully understood how cardiovascular reactivity, such as stress-induced changes in heart rate or blood pressure, relate to cerebrovascular reactivity, such as changes in cerebral blood flow, the current understanding is that both phenomena are likely to be linked to the functioning of CO<sub>2</sub>-receptors in arteries delivering blood to the brain. Chronic stimulation of these receptors due to the respiratory distress that is often present in obese populations may lead to blunted CO<sub>2</sub>-receptor responses, and this could consequently reduce cerebral blood flow. Other proposed mechanisms for reduced cerebral blood flow in obesity include cerebral ischemia, as well as changes to the structure and flexibility of the arteries in the brain, negatively impacting their ability to perfuse blood and adapt their conformation quickly to adequately supply active brain regions (Dorrance et al., 2014). Regardless of their origins, cerebrovascular changes in obesity are linked to an increased risk of cognitive decline (Nguyen, Killcross, & Jenkins, 2014) and stroke (Haley & Lawrence, 2016), suggesting cerebrovascular health has critical implications for maintaining functional independence.

The brain retains some plasticity, even into adulthood (Gage, 2004), and this plasticity can be harnessed via lifestyle behaviors, including modifying diet and increasing aerobic exercise behaviors (Erickson, Gildengers, & Butters, 2013; Phillips, 2017). Thus, it might be possible that reductions in weight—via any behavioral means—could restore cerebrovascular health. Yet, to date, most studies in this area have not been randomized clinical trials (RCT), or experimental

manipulations of eating behavior, making the causal directions unclear (i.e., whether brain deficits lead to overeating behaviors, and/or whether overeating leads to changes in the brain). An RCT has the potential for more clearly delineating causal pathways between obesity and measures of brain health by examining the effects of weight loss on brain health outcomes.

This was an ancillary study to an RCT that was designed to compare weight loss induced through diet versus diet plus exercise on measures of cardiac magnetic resonance imaging (MRI) and other health outcomes in adults with overweight or obesity. The primary aim of this ancillary study was to determine the effect of weight loss on regional cerebral blood flow (rCBF) in midlife adults with overweight and obesity. A secondary aim was to evaluate the moderating role of weight loss interventions involving exercise on rCBF. Specifically, we tested whether there was (A) an added benefit of exercise on weight loss and rCBF compared to interventions involving diet-only and (B) whether there was a dose-response effect of exercise on changes in rCBF. To accomplish these aims, we measured resting rCBF of adults with overweight and obesity both before and immediately after 12-months of a behavioral weight loss intervention involving either diet modification only, or diet plus one of two doses (high or moderate) of moderate intensity aerobic exercise.

The asymmetrical nature of the experimental design has some important implications for statistical power. Specifically, as all the treatments included a diet component, the main effect analysis was conducted using a within-subjects model. Thus, we can expect good statistical power for this analysis. On the contrary, examining the effects of exercise involve conducting comparisons between groups. Thus, these latter comparisons will inherently have lower statistical power than the former. The implications of these differences in statistical power will be discussed more in the conclusions.

The parent RCT provided a unique opportunity to compare the effects of weight loss induced by diet versus diet plus exercise on cerebral perfusion. Exercise interventions have been independently linked to improved brain health in various domains (Cotman & Berchtold, 2002), including cerebral perfusion in nonobese samples for which weight loss was not a goal (Alfini, Weiss, Nielson, Verber, & Smith, 2019; Murrell et al., 2013). This current study provides an opportunity to examine whether weight loss improves cerebral perfusion and whether the inclusion of exercise further enhances the effect. In the present study, we predicted that (1) all intervention groups would demonstrate global increases in rCBF, mostly in areas known to be susceptible to obesity-related dysfunction, such as the prefrontal cortex (Lowe, Reichelt, & Hall, 2019), (2) groups exposed to exercise would show additional perfusion changes in cortical regions, such as the temporal and prefrontal cortex, known to be independently sensitive to exercise (Colcombe et al., 2006; Erickson et al., 2011), and (3) there would be a dose-response effect of exercise such that the group receiving the higher dose of exercise would show the largest increases in rCBF compared to the group receiving a lower dose of exercise or no exercise.

## 2 | METHOD

### 2.1 | Participants

One hundred twenty-five participants (82 female) were randomly recruited from a RCT (ClinicalTrials.gov NCT01500356; R01HL103646; PI: Jakicic), with the primary outcome to examine the effects of weight loss and exercise on measures of cardiac MRI (e.g., left ventricular mass, etc.). Eligible participants were between the ages of 18–55 ( $M \pm SD = 44.63 \pm 8.36$  years; Figures S1–S3) with a BMI ranging from 25 to  $<40 \text{ kg/m}^2$  ( $M \pm SD = 32.22 \pm 3.96$ ). Participants were excluded from the parent trial for the following reasons: (1) self-reporting  $\geq 60$  min per week of structured moderate-to-vigorous intensity physical activity, (2) weight loss of  $\geq 5\%$  within the prior 6 months, or a history of bariatric surgery, (3) history of cardiometabolic disease, diabetes mellitus, or cancer, (4) taking medication that could affect heart rate or blood pressure, (5) taking medication that could influence body weight, (6) treatment for psychological conditions that included medication or counseling, (7) currently pregnant, pregnant within the prior 6 months, or planning a pregnancy within the next 12 months, (8) planning on geographical relocation outside of the region within 12 months, (9) inability to comply with the components of the interventions, (10) or had a contraindication that would prohibit MRI scanning.

Eligible participants provided written informed consent and completed an MRI before, and then, following the 12-month intervention. This study was approved by the University of Pittsburgh Institutional Review Board in accordance with the Declaration of Helsinki.

### 2.2 | Physiological testing

#### 2.2.1 | Weight assessment

Weight was assessed in duplicate on a calibrated digital scale (Tanita Digital Scale, Model #WB-110A) to the nearest 0.1 kg and height was measured in duplicate on a calibrated wall-mounted stadiometer (Perspective Enterprises, Inc.) at baseline, and then, again at 6 and 12 months of the intervention. Measures of weight and height were used to compute BMI ( $\text{kg/m}^2$ ).

### 2.3 | Intervention groups

Given that the parent study recruited 383 participants, participants in the current study were recruited across 16 cohorts. Participants were randomly assigned to one of three weight loss interventions. All intervention conditions involved participants attending in-person group sessions and individual

telephone counseling sessions that focused on behavioral strategies to assist engagement in the prescribed behaviors that were to facilitate weight loss. Group sessions were conducted separately for each intervention condition to minimize potential contamination, and sessions were scheduled weekly for weeks 1 to 24, and then, approximately every other week for weeks 25–52, with each session scheduled for 30–60 min. The days for the intervention sessions were the same throughout the study once a participant was randomized and initiated the intervention. However, individual make-up sessions were scheduled if a group session was missed. Thus, the scheduling of sessions was done in a systematic manner across the entire intervention period. Individual telephone calls were scheduled for approximately every other week, which corresponded to weeks when an individual session was not scheduled, during weeks 25–52. These telephone sessions were scheduled for approximately 10 min and followed a script to address key aspects of the intervention with a focus on continued engagement in the key elements of the intervention (diet or diet plus physical activity). Additional key elements of each intervention condition are described briefly below.

#### 2.3.1 | Diet-only

Participants randomized to Diet-only (DIET) ( $N = 50$ ) were prescribed an energy restricted diet. Energy intake was prescribed at 1,200 to 1,800 kcal/d based on baseline body weight ( $<90.7 \text{ kg}$  ( $<200$  pounds) = 1,200 kcal/d;  $90.7$ – $113.4 \text{ kg}$  (200 to 250 pounds) = 1,500 kcal/d;  $113.4 \text{ kg}$  ( $>250$  pounds) = 1,800 kcal/d). To facilitate the adoption of the dietary recommendations and to provide guidance on meal options and portion sizes, participants were provided with example meal plans that were designed by a registered dietician. Participants were also permitted to self-select their food options and were provided with a calorie counter book as a reference to facilitate adjustment of portion sizes based on their food selections. Participants were instructed to record their food choices and portion sizes in a diary that was provided to them by the investigators, and to return these diaries for review by the intervention staff at each in-person intervention session. The intervention staff provided written comments on the diaries to assist the participant in adjusting their dietary choices in a manner that would facilitate weight loss or weight loss maintenance.

#### 2.3.2 | Diet + moderate exercise

Participants in Diet + moderate exercise (DIET + MODEX) ( $N = 30$ ) received the dietary intervention as described for the DIET intervention. In addition, DIET + MODEX was prescribed physical activity that progressed from 100 min/wk

to 150 min/wk by week 9 of the intervention. Participants were encouraged to engage in physical activity on 5 days/wk to achieve their weekly prescribed goal; however, participants could adjust the days/wk to accommodate their individual schedules. Each physical activity session was to be at least 10 min in duration to count toward their weekly goal, and was to be at a moderate-to-vigorous intensity, which was self-monitored using a rating of perceived exertion scale. To achieve this prescribed intensity, participants were encouraged to engage in brisk walking or other similar intensity activities (e.g., cycling, etc.), and the specific mode of physical activity was self-selected. Participants were instructed to record their physical activity in a diary that was provided to them by the investigators, and to return these diaries for review by the intervention staff at each in-person intervention session. The intervention staff provided written comments on the diaries to assist the participant in adjusting their physical activity and overcoming barriers in an effort to maximize engagement in the prescribed amount of physical activity.

### 2.3.3 | Diet + high exercise

Participants in Diet + high exercise (DIET + HIGHEX) ( $N = 45$ ) received the dietary intervention as described for the DIET intervention. In addition, the DIET + HIGHEX group was prescribed physical activity that progressed from 100 to 250 min/wk by week 25 of the intervention. All other aspects of the physical activity intervention for DIET + HIGHEX were similar to what is described above for DIET + MODEX.

## 2.4 | MRI

### 2.4.1 | Acquisition

To quantify rCBF, we employed pseudo-continuous arterial spin labeling (pcASL), a perfusion-weighted MRI technique. All MRI data were acquired with a Siemens 3.0 Tesla MR system (Magnetom Trio Tim Syngo, Munich, Germany). A 32-channel head coil was used for radio frequency (RF) transmission and reception. Foam padding was positioned within the head coil to minimize patient motion. A high-resolution T1-weighted anatomical image was acquired for co-registration with the following sequence parameters: Magnetization Prepared Rapid Acquisition of Gradient Echo (MPRAGE), matrix = 256, field-of-view (FOV) = 250 mm, voxel size =  $1.0 \times 1.0 \times 1.0$  mm, slices = 192 (sagittal plane, acquired left to right), slice thickness = 1.0 mm, repetition time (TR) = 1900 ms, echo time (TE) = 2.93 ms, inversion time (TI) = 900 ms, flip angle =  $9^\circ$ , and sequence duration = 4:26 min. Perfusion-weighted images were collected using a multi-slice pcASL protocol for perfusion

quantification with the following parameters (Jung, Wong, & Liu, 2010): matrix size = 64, FOV = 220 mm, voxel size =  $3.40 \times 3.40 \times 5.0$  mm, slices = 20 (axial plane, acquired in ascending order), slice thickness = 5.0 mm, gap between slices = 1 mm, single slice acquisition time = 48 ms, label duration = 1,500 ms, post-label delay = 1,500 ms, TR/TE = 4090/21 ms, volumes = 80, number of label/control pairs = 40, flip angle =  $90^\circ$ , RF blocks = 80, RF pulses = 20, gap between pulses = 360  $\mu$ s, bandwidth = 2,298 Hz/Px, and sequence duration = 5:35 min.

### 2.4.2 | Preprocessing

Once reconstructed, the first 4 volumes of the image time-series were discarded to allow for signal stabilization. The truncated time-series was then realigned using the middle volume as a reference and co-registered with the T1-weighted anatomy (flirt; FMRIB Software Library version 5.0.9, Oxford, UK) (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). The time-series was subsequently visually inspected for proper alignment. Partial volume estimates were derived from the T1-weighted anatomy using FSL's Fully Automated Segmentation Toolbox (FAST; Zhang, Brady, & Smith, 2001). These high-resolution tissue-type maps were used for partial volume correction, nuisance signal regression, and tissue-specific perfusion quantification.

### 2.4.3 | Perfusion quantification

FSL's Bayesian Inference for Arterial Spin Labeling toolbox (BASIL; Chappell, Groves, Whitcher, & Woolrich, 2009) was used for perfusion quantification. First, an rCBF image was generated from the co-registered time-series using pairwise tag-control subtraction (asl\_file). Although some studies suggest that surround subtraction methods may be helpful for creating perfusion images (Liu & Wong, 2005; Lu, Donahue, & Zijl, 2006), simple tag-control subtraction, such as that applied via BASIL's asl\_file option, is the most common and widely published method of generating the difference image (e.g., Alfini et al., 2019; Chaddock-Heyman et al., 2016; Detre, Rao, Wang, Chen, & Wang, 2012). Tag-control subtraction was, therefore, the method chosen to quantify perfusion in the present study. The images were adjusted for slice-time delay. Then, BASIL's oxford\_asl command was run with the partial volume and spatial correction options turned on to further control for spurious signals (Chappell et al., 2011; Groves, Chappell, & Woolrich, 2009). The cerebral spinal fluid image from FAST was designated as the tissue reference for nuisance regression. This step also corrected the proton density image to adjust for potential errors in the blood brain partition coefficient and applied a ventricular mask to the corrected image

to isolate and compute the magnetization equilibrium ( $M_0$ ) of the white and gray matter tissue. The  $M_0$  value was used to approximate the  $M_0$  of the arterial blood and convert the relative rCBF values into absolute units of ml/100 g/min (asl\_calib). Finally, the calibrated images were normalized to MNI space. Volumes from each person, from each time point were combined into separate 4D files for group level statistical analyses. This resulted in a baseline and follow-up perfusion map for each participant. Perfusion change images were also generated for each person by subtracting their follow-up rCBF image from their baseline image. Change images were also combined into a 4D file for statistical analyses. rCBF scans at both time points were successfully acquired on 109 participants. Of these, 107 were of useable quality following preprocessing. Thus, the final sample size for the present analyses is  $N = 107$ .

## 2.5 | Planned analyses

We used an intent-to-treat approach in all analyses, such that everyone was invited back for a follow-up scan, regardless of their status in the study (e.g., still enrolled versus withdrawn) or adherence. Our primary aim was to test, regardless of group assignment, any changes in cerebral blood flow over the course of the 12-month intervention. Due to the voluntary nature of the MRI portion of the study, sample size for the DIET + MODEX group ( $N = 25$ ) was by chance much smaller than for the DIET ( $N = 42$ ) and DIET + HIGHEX ( $N = 40$ ) groups. For analyses addressing our second aim, that is, to examine whether diet combined with exercise has greater effects on rCBF than diet-only, the two exercise groups were combined into an “exercise exposure” group for analyses. To address the final aim, that is, examining dose-response effects of exercise exposure on rCBF, all three groups were assessed separately. The DIET and exercise groups were well-matched on key demographic and health characteristics at baseline ( $ps > .20$ ; Table 1).

### 2.5.1 | Intervention outcomes

The effectiveness of the intervention on the primary physiological outcome, weight, was assessed via a mixed effects

analysis of variance (ANOVA). Group (exercise exposure, DIET) was included as the between-subjects factor and time (baseline, follow-up) was the repeated measures factor. We then repeated this ANOVA using all three group assignments (DIET, DIET + MODEX, DIET + HIGHEX) to examine possible dose-response effects on weight.

### 2.5.2 | Examining main effect of weight loss interventions on perfusion

To address our primary aim, we examined main effects of time on changes in rCBF. To do this, a voxelwise analysis of covariance (ANCOVA) was conducted in `fsl_glm` in which rCBF change images were entered as the dependent variable. Age and sex were included as covariates. Results were corrected for multiple comparisons using FSL's threshold-free cluster enhancement (tfce). Based on the smoothing parameters of the data and size of the sample brain mask, the tfce method revealed that clusters of at least  $k = 270$  voxels survived whole brain correction at a threshold of  $p < .01$ .

### 2.5.3 | Examining moderating effects of exercise

Next, we examined whether the rCBF changes differed by exercise exposure. This was done by adding group assignment (DIET, exercise exposure) as an additional explanatory variable into the voxelwise ANCOVA model described above. This approach was used to test whether changes in rCBF, as reflected in the rCBF change images, were moderated by group assignment (equivalent to a Group x Time interaction). The main contrasts of interest from this analysis were the DIET > exercise exposure and exercise exposure > DIET. Results were corrected for multiple comparisons at an alpha of  $p < .01$ .

To examine the dose-response effects of exercise exposure, the same voxelwise ANCOVA was conducted again with the group assignment factor having three levels (DIET, DIET + MODEX, DIET + HIGHEX).

**TABLE 1** Characteristics of intervention groups

Measure	DIET $M$ ( $SD$ )	Diet + MODEX $M$ ( $SD$ )	Diet + HIGHEX $M$ ( $SD$ )	Exercise exposure $M$ ( $SD$ )
$N$	42	25	40	65
Age	43.24 (8.7)	45.44 (7.9)	45.58 (8.3)	45.52 (8.1)
% Female	76%	72%	80%	77%
BMI	32.26 (3.6)	32.16 (4.4)	32.22 (4.1)	32.20 (4.2)
Weight (kg)	90.67 (15.4)	90.84 (15.1)	91.20 (13.1)	91.06 (13.8)

### 3 | RESULTS

#### 3.1 | Missing data

Of the 125 subjects initially enrolled in this study, 107 (86%) successfully completed both MRI scans and had pcASL data of useable quality for analysis. The number of missing data points from the original sample were as follows: DIET:  $N = 8$ ; DIET + MODEX:  $N = 5$ ; DIET + HIGHEX:  $N = 5$ . A chi square of the complete:incomplete rates between groups was not significant ( $p = .68$ ), suggesting the proportion of missing data did not differ by group assignment. Moreover, a comparison of the subsample who did not successfully complete the follow-up MRI to the final analyzed sample revealed no differences in age, baseline weight (kg), years of education, or percent females. Based on the demographics, our results suggest that missing data are likely missing at random, however, we cannot rule out the possibility that other unmeasured characteristics related to the ability and motivation to maintain the exercise levels are not missing at random.

To confirm intervention-related physical activity levels, a modified Paffenbarger Physical Activity Questionnaire (Paffenbarger, Blair, Lee, & Hyde, 1993) was used in the parent study to assess physical activity before and after the intervention. For the 107 participants included in the present analyses, the change in physical activity from baseline to 12 months was  $65.44 \pm 74.18$  to  $78.87 \pm 105.99$  min/wk in the DIET group,  $92.22 \pm 122.33$  to  $191.85 \pm 129.02$  min/wk in the DIET + MODEX group, and  $67.88 \pm 91.64$  to  $255.81 \pm 142.03$  min/wk in the DIET + HIGHEX group ( $p$  values: group  $< .001$ , time  $< .001$ , Group  $\times$  Time  $< .001$ ). Thus, the pattern of change in physical activity in the three intervention conditions was consistent with the prescribed amounts for each group.

#### 3.2 | Intervention effects

The mixed effects ANOVA on weight with group (exercise exposure versus DIET) as the explanatory variable revealed a main effect of time, demonstrating that the weight loss intervention was effective at reducing weight,  $F(1,104) = 166.46$ ,  $p < .001$  (Table 2). On average, participants lost 10.13 (7.77) kg during the intervention, which corresponded to a 10% ( $\pm 8.81$ ) reduction in average body weight. There were

**TABLE 2** Intervention outcomes

Intervention group	Baseline weight (kg) $M$ ( $SD$ )	Follow-up weight (kg) $M$ ( $SD$ )
Exercise exposure	91.06 (13.8)	80.58 (14.0)
Diet-only	90.41 (15.5)	80.82 (14.33)

no other effects or interactions with group, suggesting that weight change was not moderated by participation in exercise (Table 2). There was also no evidence of a dose-response effect of exercise when this same ANOVA was repeated with group as a 3-level factor ( $p = .376$ ).

#### 3.3 | Main effects of time on perfusion

Consistent with our predictions, the 12-month intervention increased rCBF. Specifically, the results of the voxelwise ANCOVA on rCBF change maps revealed significant main effects of time in two large clusters located in the frontal cortex ( $k = 49,844$ ; peak MNI  $x, y, z = -8, 60, -4$ ) and lateral occipital cortex ( $k = 640$ , peak MNI  $x, y, z = 48, -66, -12$ ) (Table 3). The nature of these effects was such that rCBF increased from the baseline to follow-up. A spherical region of interest (ROI) of 10 mm diameter was created around the frontal pole peak coordinates and graphed for illustration purposes (Figure 1).

#### 3.4 | Moderating effects of exercise exposure

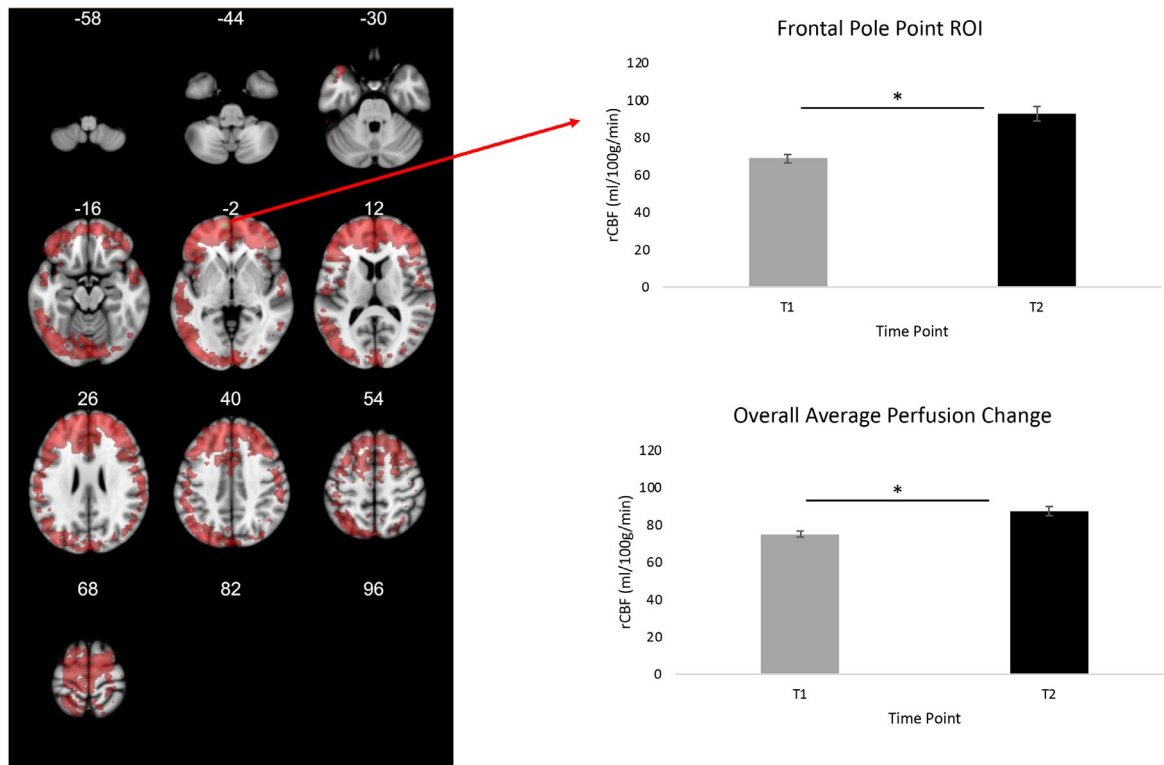
Contrary to our predictions, we found no evidence that exercise exposure moderated the effect of the intervention on rCBF. That is, no clusters survived correction in the exercise-exposure  $>$  DIET, or the reverse contrast from the voxelwise ANCOVA. We also found no evidence of a dose-response effect; there were no surviving clusters in the dose-response voxelwise ANCOVA and associated contrasts. For this reason, the exercise exposure group categorization was used for the post hoc exploratory analyses reported below.

#### 3.5 | Exploratory examination of exercise effects

Given our a priori hypothesis regarding the moderating effect of exercise and the fact that a nearly 4-fold increase in power is necessary to detect an interaction (Leon & Heo, 2009), we

**TABLE 3** Peak coordinates of clusters showing main effects of time on rCBF. Local maxima are also shown

Cluster	$k$	Region	MNI $x,y,z$	Peak $z$
1	49,844	Frontal pole	-8, 60, -4	6.48
		Cingulate gyrus	10, 46, 14	5.81
2	640	Lateral occipital gyrus	48, -66, -12	3.9
		Middle temporal gyrus	56, -52, -2	3.59



**FIGURE 1** Collapsed across group and controlling for age and sex, changes in rCBF were observed across the brain with peaks in the lateral occipital cortex and frontal pole ( $p < .01$ ) (left). A representative plot extracting rCBF from a spherical point region of interest (ROI) of 10 mm diameter and centered around the frontal pole peak is shown at top right, whereas a plot extracting the average rCBF from the entire cluster meeting significance is shown at right bottom

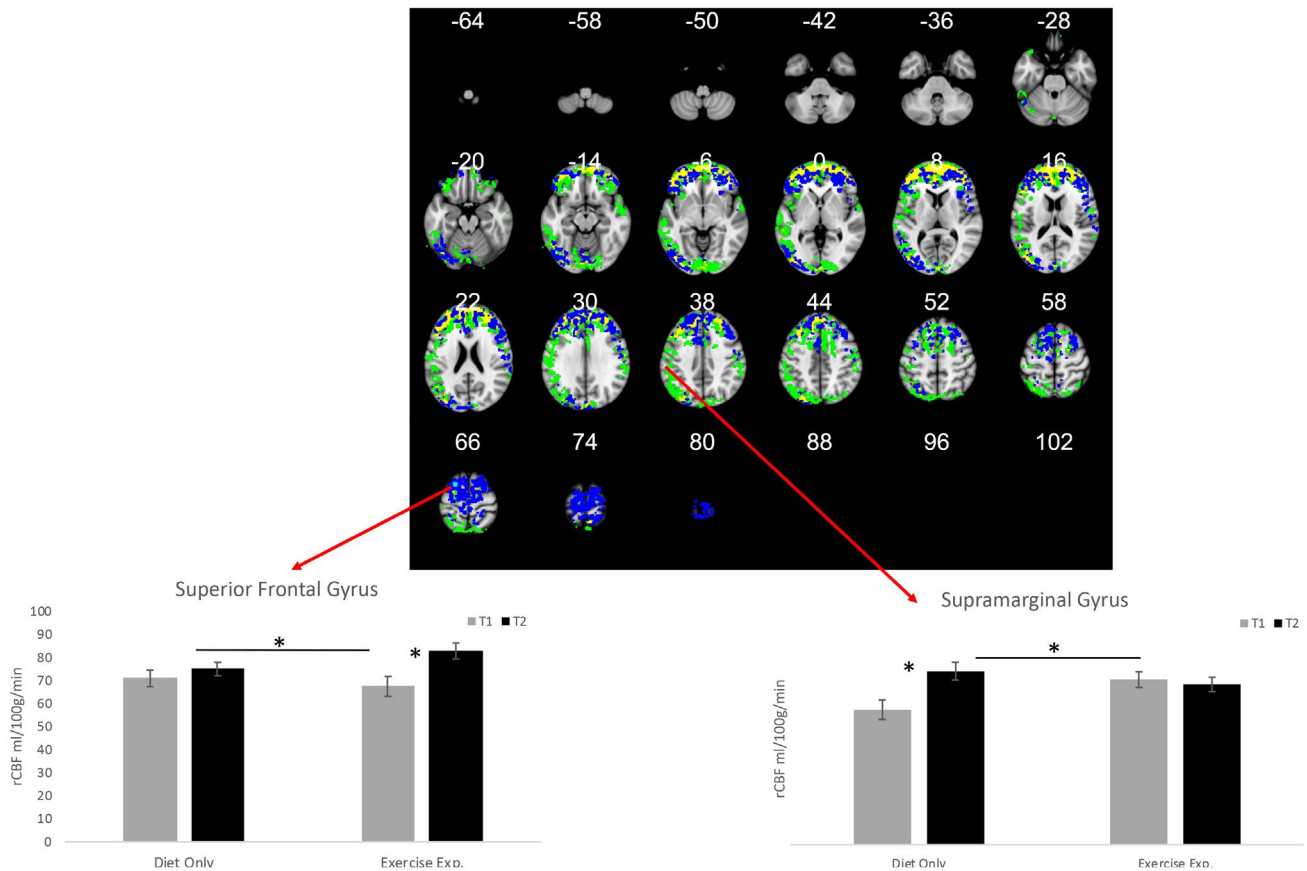
conducted exploratory  $t$  tests *within* the DIET and exercise exposure groups using the rCBF change maps. This allowed us to further test for the possibility that exercise exposure moderated the changes in rCBF and avoid the possibility of Type II error. For each group separately, a voxelwise  $t$  test was conducted in `fsl_glm` in which rCBF change images were entered as the dependent variable. Age and sex were included as covariates. Results were corrected for multiple comparisons at  $p < .01$ . We then conducted conjunction and disjunction analyses that identified the regions that were uniquely changing across the 12-month intervention for each group, as well as those overlapping across groups. Finally, we created spherical ROIs of 10 mm diameter around representative peaks for each group, extracted rCBF values in these regions from each person, from each time point, and conducted exploratory ANCOVAs in SPSS to test for interaction effects.

The conjunction/disjunction analysis revealed both overlapping and distinct clusters in which rCBF changed following the intervention (Figure 2 top). rCBF values were extracted from representative nonoverlapping clusters for each group using spherical ROIs of 10 mm diameter to examine possible interactions (Figure 2 bottom, Table 4). A representative cluster located in the superior frontal gyrus (SFG) showed changes in the exercise exposure but not DIET group, whereas a cluster in the supramarginal gyrus showed

the opposite pattern. There was a significant interaction in the SFG,  $F(1, 105) = 4.28, p = .04$ , such that rCBF in this region changed from pre- to post-intervention for those in the exercise exposure group,  $t(65) = 4.05, p < .0001$ , but not for those in the DIET group ( $p = .24$ ). There was a significant interaction in the supramarginal gyrus,  $F(1,105) = 12.78, p < .001$ , such that rCBF increased in the DIET,  $t(41) = 5.08, p < .001$ , but did not change in the exercise exposure group ( $p = .57$ ).

### 3.6 | Exploratory examination of demographic moderators

Given the large age range of our sample and varying degree of overweight and obesity, we conducted post hoc exploratory correlations to assess whether changes in weight or perfusion were related to certain baseline characteristics (i.e., age, BMI) of participants. We found no evidence that baseline BMI was related to weight loss or changes in perfusion in the clusters identified above ( $r_s < .09, p_s > .37$ ). There were also no significant correlations between baseline age and changes in perfusion in the identified clusters ( $r_s < .05, p_s > .58$ ). However, higher baseline age was significantly correlated with greater weight loss over the intervention,  $r(106) = .23, p = .02$ . Voxelwise associations with age and



**FIGURE 2** A disjunction analysis based upon the results of exploratory  $t$  tests conducted within groups (controlling for age and sex) revealed distinct regions showing rCBF changes for each group. Changes in rCBF specific to the exercise exposure group are shown in blue, whereas changes specific to the diet-only group are shown in green (top). Regions in which both groups show overlapping changes are shown in yellow. Extracting rCBF values from representative group-specific regions of interest (ROI) revealed significant Group  $\times$  Time interactions (representative plots extracting from point ROIs shown at bottom)

BMI are also reported in Supplemental Materials (Figures S4 and S5, Tables S1 and S2).

## 4 | DISCUSSION

Our results demonstrate a remarkable degree of plasticity in the cerebrovasculature and regulatory mechanisms of rCBF in adults with overweight or obesity. In contrast with views that weight gain might have an irreversible impact on some aspects of brain health, the results we report indicate that obesity-related differences in rCBF could be significantly ameliorated by 12-months of a behavioral intervention resulting in an approximately 10% loss in bodyweight.

All of the behavioral intervention groups showed significant weight loss, and we found no evidence that weight loss was moderated by exercise exposure. Although several previous studies have reported that interventions combining diet and exercise results in greater weight loss than either strategy alone (see Washburn et al., 2014 for review), other studies have found little added benefit for weight loss in combined

diet + exercise interventions compared to diet alone (Bertz et al., 2012; Foster-Schubert et al., 2012). Possible explanations for the mixed results regarding the role of exercise in weight loss may relate to the heterogeneity across studies in exercise dose (volume and intensity) and intervention length. For example, it has been posited that exercise may promote weight loss at higher doses (i.e., intensity and volume of activity per week) and in longer-term interventions, whereas it may be more effective for weight maintenance (i.e., preventing weight gain or regain) at lower doses and in shorter-term interventions (Jakicic & Otto, 2005; Johns, Hartmann-Boyce, Jebb, & Aveyard, 2014). In addition, there is evidence that some people engage in compensatory behaviors following exercise that may undermine any effects on weight loss—for example, by increasing sedentary behavior throughout the rest of the day or by increasing calorie intake following an exercise session (Foright et al., 2018; King et al., 2007). These explanations may help explain why exercise-exposure did not moderate weight loss in our sample.

Interestingly, the benefits of exercise on rCBF do not appear to entirely depend on weight loss. Mirroring the pattern



**TABLE 4** Peak coordinates of clusters showing rCBF changes unique to each group. Local maxima are also presented

<i>k</i>	Region	MNI <i>x,y,z</i>	Peak <i>z</i>
DIET			
2005	Angular gyrus	-44, -60, 16	4.22
	Supramarginal gyrus <sup>a</sup>	-44, -48, 24	4.02
	Middle temporal gyrus	-44, -58, -2	3.95
	Lateral occipital cortex	-44, -78, 40	3.92
552	Occipital pole	4, -90, 10	3.93
	Lingual gyrus	10, -88, -6	3.58
366	Frontal pole	-30, 38, 24	3.63
	Middle frontal gyrus	-28, 34, 24	3.42
Exercise-exposed			
12,354	Precentral gyrus	-10, -32, 74	5.37
	Middle frontal gyrus	-14, 28, 62	5.29
	Cingulate	-14, 54, 2	5.23
	Frontal pole	-32, 54, 12	5.07
	Superior frontal gyrus <sup>a</sup>	-14, 28, 62	3.41
2,563	Occipital pole	-32, -92, 0	4.91
	Lateral occipital cortex	-46, -76, -8	4.84
345	Postcentral gyrus	58, -12, 30	4.42
	Central opercular cortex	50, 60, 41	4.13
	Precentral gyrus	52, -2, 18	4.01

<sup>a</sup>ROIs plotted for visualization purposes.

observed for weight loss, we found that the 12-month intervention increased rCBF globally, and independent of group assignment. In addition, exploratory analyses suggested that rCBF increases in several regions that were unique to both the DIET and exercise exposure groups. Consistent with our hypothesis, this pattern of results suggests that weight loss increases rCBF in certain brain regions, regardless of exercise participation. However, weight loss interventions involving exercise exposure may provide unique effects on rCBF, compared to interventions involving only diet.

Our finding that rCBF increased diffusely across the brain, regardless of group assignment, is consistent with the notion that obesity has a rather global impact on brain cerebrovascular health. For example, excess weight is linked with cerebral ischemia, as well as damage to the cerebral vasculature and blunted cerebrovascular/cardiovascular reactivity, which can alter CBF diffusely across the brain (Dorrance et al., 2014; Phillips, 2011). Fortunately, our results suggest that at least some of this damage can be reversed within 12-months. Relatedly, the majority of our sample was from a midlife age group (Supplemental Material). Arteriosclerosis often starts to manifest in midlife and is known to be exacerbated by excess weight (Jensen et al., 2014; Mao, Ait-Aissa, Lagrange, Youcef, & Louis, 2012). Thus, it is possible that individual

variability in the magnitude and severity of baseline arteriosclerosis in our sample explains some of the individual differences observed in cerebral perfusion changes. Unfortunately, data on baseline arteriosclerosis was unavailable in this study so we were unable to examine the possible moderating effects of arteriosclerosis on changes in rCBF. Other potential moderators include baseline age and BMI, both of which may be correlated with severity of arteriosclerosis. Consistent with this idea, we observed that higher age was correlated with greater weight loss, but age was not associated with greater changes in rCBF, perhaps reflecting some degree of irreversible arteriosclerosis damage in older participants. Although it is still not clear to what degree behavioral weight loss interventions can reverse vascular damage such as arteriosclerosis (Gattone & Giannuzzi, 2006; Hjerkin et al., 2006; Iris et al., 2010; Kalanuria, Nyquist, & Ling, 2012), our results support the claim that weight loss is capable of increasing brain perfusion and potentially delaying or preventing the progression of such conditions. Consideration of additional baseline participant characteristics that may moderate the effectiveness of behavioral weight loss interventions could yield insights into the mechanisms underlying interindividual differences in physiological and neural responsiveness to diet and exercise treatments and inform more personalized treatment plans.

Of note, we did not have a normal weight control group in this study, and so it is not possible to conclude whether the increases in rCBF we observed in this sample with overweight/obesity completely restored perfusion levels to those of normal weight adults. An interesting question for future research would be to determine whether there are any brain regions for which rCBF cannot be restored with weight loss, or if there are regions that only respond to more significant weight loss (i.e., greater than the ~10% initial body weight lost in this study).

Although we found no evidence that exercise moderated the impact of the weight loss intervention on rCBF via the more conservative voxelwise ANCOVA analyses, our exploratory *t* tests of rCBF changes in the DIET and exercise exposure groups separately revealed that perfusion changes in some regions varied by group assignment. Consistent with our predictions, the exercise exposure group showed rCBF changes in a variety of regions, including the predicted frontal regions (e.g., SFG), where the DIET group did not. These results suggest that compared to diet-only approaches to weight loss, interventions incorporating exercise might especially impact rCBF in frontal brain regions supporting higher-order, executive cognitive behaviors (Colcombe & Kramer, 2003). Indeed, this regional specificity is in line with the results of previous aerobic exercise interventions incorporating MRI measures, which have posited an increased sensitivity of frontal and temporal regions to aerobic exercise interventions (as well as to pathological aging processes) (see

Haeger, Costa, Schulz, & Reetz, 2019 for review). Of note, however, only a handful of prior studies have incorporated resting state ASL in the context of a randomized intervention involving exercise in humans (Burdette et al., 2010; Pereira et al., 2007; van der Kleij et al., 2018), and the results of these studies were mixed regarding changes in rCBF. In one, neither regional or global rCBF changes were detected in a small ( $N = 27$ ) sample of patients with Alzheimer's Disease following a 16-week aerobic exercise intervention compared to a usual care control group ( $N = 24$ ) (van der Kleij et al., 2018); in others, region-of-interest analyses detected rCBF changes within the hippocampus following brief (12–16 weeks) exercise interventions in older adults with subjective memory complaints (Burdette et al., 2010) or healthy younger adults (Pereira et al., 2007). Given the drastic difference in intervention designs, sample sizes, analytical approaches, and populations, it is difficult to draw any direct comparisons between these previous studies and the present study.

Contrary to our predictions, there were also regions, such as the supramarginal gyrus, where the diet-only group showed rCBF changes and the exercise exposure group did not. The reasons, mechanisms, and behavioral implications of these regional differences remain unknown, but our results suggest that there may be distinct advantages of both lifestyle interventions (diet-only versus diet combined with exercise). The regionally specific effects of the diet-only group may be surprising in light of findings from previous multimodal interventions. For example, a large cohort study called the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Ngandu et al., 2015), reported larger cognitive effects in older adults who were assigned to a multimodal intervention involving diet, exercise, cognitive training, and vascular health monitoring compared to an educational control group that received only health advice. FINGER had several key differences from the present study which makes direct comparisons difficult. First, weight loss was not a goal in FINGER as the sample was not selected to have overweight or obesity. Second, FINGER did not include a diet-only comparison group, nor was it able to disentangle the unique contributions of each component of the multimodal group. Studies that *have* compared a diet-only to a multimodal intervention involving exercise have not included brain imaging (see Milgram et al., 2005 for relevant animal model). Brain imaging measures were also not collected in FINGER. Therefore, the fact that larger cognitive effects were observed for the multimodal intervention group compared to the control group is not necessarily discrepant with our finding of unique and overlapping cerebral perfusion changes in the diet-only versus diet + exercise groups. It is plausible, for example, that changes to rCBF or other brain measures precede those detected in behavior (Stillman et al., 2017).

Our finding of several regionally distinct perfusion changes resulting from the diet-only intervention is consistent

with physiological findings from previous single-component dietary interventions (for review see Joris, Mensink, Adam, & Liu, 2018). For example, a large randomized trial of 459 adults observed that dietary modification, particularly a Mediterranean diet, was effective at reducing blood pressure, independent of weight loss or changes in sodium intake (Svetkey et al., 1999). Although this study did not include brain imaging, these results are consistent with ours in that they suggest dietary interventions alone can have effects on vascular health. Indeed, shorter-term dietary interventions involving supplemented nitrite (Clifford et al., 2019), polyphenols (Rangel-Huerta, Pastor-Villaescusa, Aguilera, & Gil, 2015), or dietary fatty acids (Haast & Kiliaan, 2015) have been shown to increase cerebral perfusion, possibly due to their beneficial effects on vascular endothelial functioning (Joris et al., 2018).

## 4.1 | Limitations

There are a number of limitations of this study. First, our design did not include a no-contact control group; that is, all groups were part of a dietary modification intervention. It is therefore not possible to rule out the possibility that rCBF changed over the course of the 12-months for reasons other than the behavioral intervention itself. However, exploratory analyses found different rCBF changes in the group exposed to exercise compared to that exposed to diet-only, suggesting that these brain changes were indeed related to the intervention.

Another limitation was that although our results suggest that exposure to exercise (in addition to diet) during weight loss leads to additional rCBF changes, these changes were perhaps not as robust as they would have been with larger sample sizes that would have allowed for a better powered dose-response analysis. In addition, we cannot rule out certain compensatory behaviors of those in the exercise groups that may have altered the pattern of results. For example, although weekly diaries were used as an intervention tool given that self-monitoring and feedback are key aspects of a behavioral weight loss interventions (e.g., Burke, Wang, & Sevick, 2011), the dietary information included in these diaries were not intended to be used to quantify diet quality. Therefore, information on whether participants in the exercise groups may have compensated for their increased activity levels with additional caloric intake (which may have sabotaged any moderating effect on weight and rCBF) is not available. For this reason, diet quality should be a focus of future studies. Finally, we did not include a longer-term follow-up assessment of the groups in order to examine whether exposure to exercise during weight loss leads to additional beneficial outcomes (e.g., better weight maintenance). It is possible, for example, that greater benefits of participation in

exercise during weight loss may be observed in months/years following the intervention.

Third, our exploratory analyses of rCBF changes within groups revealed some regions where rCBF changes differed by exercise exposure compared to DIET. However, none of these regions survived correction in the overall voxel-wise ANCOVA in which group contrasts were examined. Given that ~4 fold increase in statistical power is needed to test an interaction effect (Leon & Heo, 2009), this pattern suggests that we may have been insufficiently powered to test this interaction. The asymmetrical nature of our experimental design may have played a role here since the main effect analysis was conducted using a within-subjects model, but the effects of exercise involve conducting comparisons between groups. Thus, the group comparisons were inherently lower in statistical power. Thus, the group differences in rCBF changes we reported as part of the exploratory analyses should be interpreted with caution and larger studies will be necessary to more definitively test for moderators.

A final limitation relates to the modality of neuroimaging data we report. Arterial spin labeling MRI is among the noisiest of modalities. As such, special consideration must be taken to improve signal-to-noise ratios (SNR) in perfusion quantification. Our processing pipeline in the FSL BASIL toolbox included several procedures designed to improve SNR (i.e., spatial regularization, partial volume correction, CSF signal regression, etc.). We also took steps to further minimize noise artifacts by collecting and processing each group's data in exactly the same manner and on the same scanner at each time point. We are therefore confident in the effects we report. However, it should be noted that many alternative preprocessing pipelines exist (e.g., to minimize BOLD signal noise; Liu & Wong, 2005; Lu et al., 2006) and may change the perfusion values slightly. However, as such acquisition noise is expected to be constant across time and groups when using the same procedures and scanner, this type of variability in preprocessing pipelines would not be expected to influence the difference scores we report.

## 4.2 | Conclusions

The results of this study suggest that rCBF in adults with overweight and obesity can be modified via weight loss. A behavioral intervention lasting only 12-months and resulting in a 10% reduction in body weight (0.83% per month) was able to accomplish these changes. These findings could have far reaching implications for designing interventions for other groups at increased cerebrovascular risk (e.g., stroke or traumatic brain injury patients) to restore rCBF to key brain regions.

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## SUPPORTING INFORMATION

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

FIGURE S1 Age distribution of sample, collapsed across group assignment

FIGURE S2 Age distribution of sample, split by exercise-exposure group. The exercise-exposure group contains participants randomly assigned to either the MODEX + DIET and HIGHEX + DIET intervention groups, while the DIET group contains participants assigned to the diet-only group

FIGURE S3 Age distribution of sample, split by exercise dose

FIGURE S4 Regions showing positive association between baseline age and changes in rCBF. A scatter plot is shown for a representative cluster from the table above (cluster 2)

FIGURE S5 Regions showing positive association between baseline BMI and changes in rCBF. A scatter plot is shown for a representative cluster from the table above (cluster 2)

TABLE S1 Clusters showing association between higher baseline age and larger changes in rCBF over the intervention. Results were corrected for multiple comparisons at  $p < .05$ .

A representative cluster (denoted with an \*) is plotted below. There were no negative associations between baseline age and changes in rCBF

TABLE S2 Clusters showing association between higher baseline BMI and larger changes in rCBF over the intervention. Results were corrected for multiple comparisons at  $p < .05$ . A representative cluster (denoted with an \*) is plotted below. There were no negative associations between baseline BMI and changes in rCBF

**How to cite this article:** Stillman CM, Jakicic J, Rogers R, et al. Changes in cerebral perfusion following a 12-month exercise and diet intervention. *Psychophysiology*. 2020;00:e13589. <https://doi.org/10.1111/psyp.13589>