Metabolic and vascular risk factors are associated with reduced cerebral blood flow and poorer midlife memory performance

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Abstract
Midlife metabolic and vascular risk factors (MVRFs) predict cognitive decline and dementia; however, these risk factors tend to overlap, and the mechanisms underlying their effects on cognitive performance are not well understood. This cross-sectional study investigates the contributions of MVRFs to regional cerebral blood flow (CBF) and verbal learning & memory among middle-aged adults. We used partial least squares (PLS) analysis to create latent risk factor profiles and examine their associations to CBF in 93 regions of interest among 451 participants (age 50.3 ± 3.5 years) of the Coronary Artery Risk Development in Young Adults. This multivariate analysis revealed regional CBF was lower in relation to obesity (higher body mass index and waist circumference), dysregulated glucose homeostasis (higher fasting glucose, oral glucose tolerance, and higher fasting insulin), and adverse fasting lipid profile (lower high-density lipoprotein cholesterol and higher triglycerides). In a sensitivity analysis, we found that significant associations between MVRFs and CBF were prominent in the hypertension-medicated subgroup. In a mediation model, the PLS-based MVRFs profile was associated with memory performance (rey auditory verbal learning test); however, CBF was not a significant mediator of this association. The
resolves captures an adverse midlife metabolic profile that might set the stage for incipient dementia and contribute to widespread changes in CBF.

KEYWORDS
blood pressure, body mass index, cerebral blood flow, fasting glucose, memory, partial least squares, vascular risk factors

1 | INTRODUCTION

Obesity, diabetes, high blood pressure, and altered lipids are commonly comorbid metabolic and vascular risk factors (MVRFs), often conceptualized collectively as the “metabolic syndrome.” Each of these variables is associated with an increased risk of dementia. The impacts of midlife obesity and impaired glucose tolerance stretch over 25 years of follow-up (Curb et al., 1999; Qiu & Fratiglioni, 2015; Whitmer, Guderson, Barrett-Connor, Quesenberry, & Yaffe, 2005). Data-driven approaches suggest that vascular changes are among the earliest to occur in incipient Alzheimer’s disease (AD) (Iturria-Medina et al., 2016). Accordingly, trials designed to prevent or delay cognitive decline focus increasingly on managing MVRFs (Chuang et al., 2016), but the impacts of these MVRFs on the brain and cognitive decline remain incompletely understood.

MVRFs at midlife, a critical turning point in brain aging, likely contribute to endothelial dysfunction, inflammatory processes, and to morphological and functional alterations to the arteriolar walls (Joutel et al., 2010). MVRFs are thought to induce changes in neural circuits, such as the prefrontal and ventral striatal regions involved in food reward processing, self-regulation and stress (Dunn et al., 2012; Ottino-González et al., 2017), which could influence regional neurovascular metabolism and hence, CBF. Evidence in support of brain changes in relation to MVRFs is however mixed (Cavalieri et al., 2010). Among the MVRFs, the most is known about the effects of hypertension and diabetes on the brain. A meta-analysis on the role of blood pressure implicates loss of brain tissue in the frontal and temporal lobes (Beauchet et al., 2013; Schneider et al., 2017). A case-control comparison of people with and without metabolic syndrome reported reduced white matter, in addition to gray matter (Sala et al., 2013). Another study reported that it is visceral adipose tissue that circumferential and triglycerides were associated with reduced CBF (Birdsill et al., 2013). Yet, the influences of particular components of the metabolic syndrome—obesity, dyslipidemia, dysregulated glucose homeostasis and hypertension—have yet to be adequately characterized. To examine these inter-related MVRFs, we employ multivariate partial least squares, an analytical approach that is designed to handle collinear independent variables (McIntosh, Bookstein, Haxby, & Grady, 1996). The outcome measures in this multivariate PLS model are the CBF values from within regions of interest (ROI) in a sample of adults that are 50 years old. We hypothesize there will be at least one latent variable that relates MVRFs and CBF, and specifically, that a higher MVRF burden will be associated with lower regional CBF levels. Since this cohort has a sizable subgroup of participants with hypertension (Launer et al., 2015), we conducted a sensitivity analysis stratified by hypertension status. To provide clinical context, we tested if CBF mediated an indirect relationship between MVRF burden and memory performance, simultaneously testing a direct relationship between MVRF burden and memory (i.e., one that is not mediated by CBF).

2 | METHODS

2.1 | Participants

Data in this study are from a sub-sample of black and white men and women who participated in the community-based coronary artery risk development in young adults (CARDIA) study, examined at year-25. CARDIA is a longitudinal study of the development and determinants of cardiovascular disease in 5115 young adults who were aged 18–30 years at baseline in 1985–1986. The community-based sample for the current study was recruited from three US cities (Birmingham, Minneapolis, and Oakland) to be approximately balanced by sex, age (18–24 years and 25–30 years), race (white, black), and education (high school, >high school) (Friedman et al., 1988).

Between 2010 and 2011, 72% of the surviving CARDIA cohort attended the year-25 exam assessments. Participants provided written informed consent at each exam, and institutional review boards from each field center and the coordinating center (University of Minnesota Institutional Review Board, Kaiser Permanente Northern California Institutional Review Board) approved this study annually. A sub-sample of CARDIA participants underwent MRI scanning at year 25 to characterize brain morphology, pathology, physiology, and function. Other standard exclusions for the MRI sub-study were applied,
which included implants not safe at 3.0 T and physical body size of participants precluding comfortable positioning in the magnet bore.

2.2 | Clinical assessments

Risk factor measures were obtained at the 25-year follow-up, and were characterized by: (a) body mass index (BMI; from height and weight) and waist circumference to index obesity; (b) diastolic and systolic blood pressure were assessed using a digital blood pressure monitor (Omron HEM-907XL; Online Fitness, CA); (c) participants were instructed to fast and abstain from smoking or heavy physical exertion for 12 hr prior to the blood draw to measure fasting glucose and insulin levels. An oral glucose tolerance test (OGTT) was performed to measure the acute (2-hr) blood glucose response to a high glucose drink; (d) blood samples were also analyzed for high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglyceride concentrations. Diabetes was defined following the American Diabetes Association criteria for levels of fasting, non-fasting, or postprandial OGTT results, HbA1c percent, or use of anti-diabetes medication (American Diabetes Association, 2011).

2.3 | Cognitive assessments

To index memory performance, we used the Rey auditory verbal learning test (RAVLT) as the primary cognitive measure. The RAVLT was tabulated as five scores from verbal learning trials, and two free recall trials, the first after a distractor list, and the second after a 30-min delay. This test has demonstrated utility in type 2 diabetes, obesity and/or cardiovascular disease (Cournot et al., 2006; MacIntosh et al., 2015; Punthakee et al., 2012).

2.4 | Brain MRI

MR imaging consisted of T1-weighted anatomical imaging and two CBF techniques: pseudo-continuous arterial spin labeling (ASL) was used to measure whole brain and regional CBF; after the ASL sequence, phase-contrast angiography was performed and these data were used to provide a secondary estimate for whole brain CBF in the current study. MRI details are described previously (Launer et al., 2015). T1-weighted images were acquired in three-dimensions using an MPRAGE sequence, along the sagittal plane, and with the following parameters: voxel = 1 x 1 x 1 mm³, TR/TE/TI = 1900/29/900 ms, matrix = 256 x 256, slices = 176, FOV = 250 mm, flip angle = 90°, GRAPPA = 2, and bandwidth = 170 Hz/pixel. ASL used gradient-echo echo planar imaging with repetition time (TR) and echo time (TE) of 4 s, 11 ms, respectively. ASL was performed with a label duration of 1.48 s, offset by a fixed distance of 90 mm from the central ASL imaging volume, and post labeling delay (PLD) to the most inferior slice by 1.5 s, with a radio-frequency pulse gap of 0.36 ms, pulse duration of 0.5 ms, and mean z-direction gradient of 0.6 mT/m, and no background suppression. Forty label and control pairs were acquired for a 4 s, 11 ms, respectively. ASL was performed with a label duration of 1.48 s, offset by a fixed distance of 90 mm from the central ASL imaging volume, and post labeling delay (PLD) to the most inferior slice by 1.5 s, with a radio-frequency pulse gap of 0.36 ms, pulse duration of 0.5 ms, and mean z-direction gradient of 0.6 mT/m, and no background suppression. Forty label and control pairs were acquired for a 5 min and 20 s acquisition. Other imaging parameters include: voxels = 3.4 x 3.4 x 5 mm³, matrix = 64 x 64, flip angle = 90°, FOV = 220 mm, bandwidth = 3.004 Hz/pixel, echo spacing = 0.44 ms and an EPI factor = 64. Twenty slices with a distance factor of 20% were acquired from inferior to superior in a sequential order. Phase-contrast angiography was prescribed at the level of ASL labeling plane (Dolui et al., 2016). Angiographic data were acquired at eight phases within a cardiac cycle with a maximum velocity encoding of 100 cm/s, voxels = 0.8 x 0.8 x 5.0 mm³, FOV = 20 cm, TR = 140 ms, TE = 10 ms, flip angle = 15° and bandwidth = 260 Hz/pixel. As in (Dolui et al., 2016) and as a quality control procedure, we used the phase contrast data to estimate whole brain CBF, normalized by brain volume. We compared this estimate against total CBF from ASL.

2.5 | Image processing

MR images were processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and in-house programs developed in MATLAB (Mathworks Inc., Natick, MA). Raw ASL label-control time series data were first motion corrected followed by removal of residual motion (Wang, 2012). Images were smoothed using an isotropic Gaussian kernel with full-width-half-max of 5 mm. Thereafter, a CBF time series was obtained by pairwise control-label subtraction. We converted the CBF image intensity to absolute units after averaging the difference images and used the ASL control image as the estimate of the equilibrium magnetization (Alsop et al., 2014).

CBF images were effectively down sampled to participant-specific and anatomy defined gray matter ROI, based probabilistic segmentation of T1 images using SPM8. This step was chosen to reduce the number of output variables that were used in the PLS. A total of 93 ROIs were extracted using a Talairach-based brain anatomy template and a previously developed segmentation algorithm (Goldszal et al., 1998). These data were represented in a matrix grid (i.e., an 8 x 12 matrix with three empty cells). Total brain volume was based on tissue segmentation maps for gray and white matter maps. Whole brain ASL was computed as mean CBF across all ROIs. Phase contrast angiography data were analyzed by a semiautomated procedure of isolating the internal carotid and vertebral arteries and growing the lumen mask using a flood-filling algorithm of neighboring voxels (Dolui et al., 2016). Blood flow velocity was obtained for each of the eight phases at each voxel in the mask, which was then multiplied by cross-sectional area to produce a volume flow rate estimate. Global estimates were adjusted by brain density (assumed to be 1.06 g/ml) (Aslan et al., 2010) to produce CBF with units of ml/100 g/min. The ratio of phase contrast to ASL whole brain CBF estimates was used to evaluate potential bias. The whole brain CBF ratio was not influenced by BMI (t = −0.67, df = 380, r = .034, p = .50; Figure S1), thus BMI did not confound the ASL measurement.

2.6 | Statistical analyses

Clinical variables and outcomes were summarized using counts and percentages or means and SDs. Regional CBF estimates were adjusted for age, sex, years of education, and site. Also a priori, CBF was adjusted for total brain volume to account for global tissue volume.
and further account for partial volume effects. The PLS model included CBF ROI as dependent and MVRFs as independent variables.

PLS was implemented in Matlab and software is available from Rotman Research Institute (A. R. McIntosh et al., 1996; A. R. McIntosh & Lobaugh, 2004). In PLS models, dependent and independent variables are combined into one cross-correlation matrix. The objective is to reduce the dimensionality of this matrix, which in this case used singular value decomposition, a technique similar to principal component analysis. This procedure generates a set of orthogonal latent variables (consisting of pairs of singular matrices and singular values per latent variable). A summary metric, that is, a brain score, was computed for each latent variable (the matrix manipulation was a dot product between the singular images and the original data matrix). Latent variables were evaluated for statistical significance by nonparametric permutation testing. A latent variable was deemed significant if the permutations revealed a p-value threshold, that is, p < .05. The bootstrap procedure is designed to determine which ROIs show the latent variable effects. As described previously (A. R. McIntosh & Lobaugh, 2004), no correction for multiple comparisons is necessary since no statistical test is performed for this step. An absolute value of the bootstrapping ratio (BSR > 2.0) was used as the threshold for individual ROIs.

To support the primary hypothesis, sensitivity and exploratory analyses were performed. In a sensitivity analysis, the PLS model was run in subgroups based on treatment for a diagnosis of hypertension as a potential source of heterogeneity. A second sensitivity analysis was also run after additional adjusting CBF data by race (i.e., black and white). In an exploratory analysis, we used three summary measures to conduct a mediation analysis (Sobel function in the Multilevel package in R, version 3.3.3). This mediation model tested for direct and indirect associations between MVRFs and memory performance; the indirect association included CBF as a potential mediator. The MVRF composite consisted of the primary factor among the MVRF variables identified by the PLS. The CBF composite was the average across the significant ROIs identified by the PLS—covariate adjustments as previously. The third variable was the aggregate score from the RAVLT memory performance test, which was extracted as a single factor score in a factor analysis, after adjusting for age, sex, years of education, and site.

3 | RESULTS

There were 451 CARDIA participants (220 male/231 female) included in this study. Table 1 shows sample details. Many of the metabolic and vascular risk factors showed a high degree of bivariate correlation, except for LDL cholesterol, which was significantly related only to HDL cholesterol (Figure 1). A representative CBF image is provided in Figure 2.

3.1 | PLS analysis

PLS analysis produced one significant latent variable (p = .005) that explained 79% of the variance between the CBF ROIs (outputs) and the MVRFs (Figure 3). BMI, waist circumference, fasting glucose, OGTT, insulin, HDL, and triglycerides each contributed significantly to this latent variable. Each variable showed a partial correlation with CBF that was an inverse relationship, except for HDL cholesterol that showed a positive partial correlation. The latent variable, indexing a composite metabolic risk factor profile of obesity, glucose dysregulation, and dyslipidemia, was related to CBF in the ROIs provided in the Supplementary Table. The identified ROIs included regions in the temporal lobe (e.g., hippocampus, temporal pole, and superior temporal gyrus), the frontal lobe (e.g., amygdala, insula, and medial and middle frontal regions), the parietal lobe (e.g., angular gyrus, cuneus, and cingulate), the occipital lobe (e.g., lingual gyrus, lateral, inferior, and superior occipital cortex, and occipital pole), and basal ganglia (e.g., caudate, globus pallidus, and putamen).

3.2 | Mediation analysis

The mediation model is shown in Figure 4. There was a significant association between the MVRF composite score and the CBF composite (t = −2.10, p = .03). The MVRF composite was also associated with the memory composite (i.e., a direct effect with the single factor from the seven RAVLT test scores; t = −2.06, p = .03). The composite CBF was not associated with the RAVLT composite score (t = 0.46, p = .60), and there was no evidence of an indirect effect (i.e., CBF did not mediate an association between MVRFs and memory, Z-statistic = −0.45, p = .65).

3.3 | Sensitivity analyses

In a subgroup without hypertension (N = 347), a latent variable consistent with previous PLS models was seen; although this latent variable

| TABLE 1 | Demographic, metabolic syndrome, and study variables (mean ± SD, or count) |
|----------|---------------------------------------------------------------|
| Age (years) | 50.3 ± 3.5 |
| Sex (male/female) | 220/231 |
| Race (black/white) | 160/291 |
| History of hypertension (yes/no/not known) | 99/347/5 |
| History of hypercholesterolemia (yes/no/not known) | 108/328/15 |
| History of diabetes (yes/no) | 11/440 |
| Body mass index (kg/m²) | 28.2 ± 5.1 |
| Waist circumference (cm) | 90.9 ± 13.2 |
| Diastolic blood pressure (mmHg) | 73.7 ± 11.0 |
| Systolic blood pressure (mmHg) | 118.1 ± 14.5 |
| Diabetes diagnosis (no/yes) | 441/10 |
| Fasting glucose (mg/dl) | 94.3 ± 20.4 |
| Glucose tolerance test at 2-hr (mg/dl) | 104.6 ± 41.8 |
| Fasting insulin (pmol/L) | 28.0 ± 6.9 |
| High-density lipoprotein (mg/dl) | 58.9 ± 16.8 |
| Low-density lipoprotein level (mg/dl) | 115.7 ± 31.5 |
| Triglycerides (mg/dl) | 108.7 ± 62.8 |
| MRI scanning site (1/2/3) | 5/230/216 |
explained 57% of the variance, it was not significant ($p = .18$) based on the permutation-based criteria. In contrast, among those with hypertension ($N = 99$), the latent variable was significant with $p < .001$, which explained 81% of the variance (see Figure S2). Additionally, accounting for the influence of race on CBF (i.e., covarying for race a priori to the PLS model) did not affect the significant latent variable and had the effect of increasing the explained variance in the PLS model (i.e., 86%). We did observe, however, that diastolic blood pressure contributed significantly to this race-adjusted PLS model.

**FIGURE 1** A summary of the bivariate correlation coefficients between each of the metabolic and vascular risk factors. Ellipse shapes denote the direction of the correlation and numerical values are also provided in each of the corresponding correlation panels. Red color denotes positive correlation, while blue denotes negative correlation. BMI, body mass index; waist, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; GLU, fasting glucose; GLU2HR, oral glucose tolerance test; INS, insulin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TRIG: triglycerides

|       | BMI | WAIST | SBP | DBP | GLU | GLU2HR | INS | HDL | LDL | TRIG |
|-------|-----|-------|-----|-----|-----|--------|-----|-----|-----|------|
| BMI   | 0.85| 0.39  | 0.46| 0.28| 0.19| 0.22   | 0.57| −0.33| 0.05| 0.23 |
| WAIST | 0.39| 0.86  | 0.19| 0.24| 0.24| 0.62   | −0.49| 0.09 | 0.4  |      |
| SBP   | 0.46| 0.86  | 0.19| 0.24| 0.24| 0.62   | −0.49| 0.09 | 0.4  |      |
| DBP   | 0.28| 0.24  | 0.19| 0.21| 0.24| 0.62   | −0.49| 0.09 | 0.4  |      |
| GLU   | 0.72| 0.22  | 0.21| 0.21| 0.21| 0.62   | −0.21| 0.08 | 0.26 |      |
| GLU2HR| 0.25| −0.13 | −0.13| 0.21| −0.23| 0.08   | 0.26 | 0.24 |      |      |
| INS   | −0.36| 0.06 | 0.06| 0.06| 0.06| 0.06   | 0.38 | 0.38 |      |      |
| HDL   | 0.13| −0.21 | −0.43| 0.13| −0.23| 0.08   | 0.26 | 0.24 |      |      |
| LDL   | 0.13| 0.07  | 0.07| 0.07| 0.07| 0.07   | 0.38 | 0.38 |      |      |
| TRIG  | 0.24| 0.24  | 0.24| 0.24| 0.24| 0.24   | 0.24 | 0.24 |      |      |

**FIGURE 2** The left panel image shows an axial view of the absolute CBF image for a single participant. The scale bar denotes the CBF level as the image intensity (units: ml/100 g/min). The middle panel shows the corresponding T1-weighted image. The right panel is the histogram of CBF values across all participants for one ROI (i.e., the left precuneus region). CBF, cerebral blood flow; ROI, regions of interest
A cluster of metabolic and vascular risk factors explained widespread regional decrements in CBF at midlife. The PLS analysis pooled the shared variance in a principled manner to identify the set of MVRFs that were associated with CBF. The MVRF profile comprised obesity, impaired glucose homeostasis, and dyslipidemia variables. Although blood pressure did not contribute to the latent pattern associated with altered CBF in the PLS model, sensitivity analysis showed that the hypertension-medicated subgroup contributed significantly to the PLS latent variable. Exploration of these MVRFs and CBF data in relation to memory suggested a direct association between MVRFs and memory, but an indirect effect mediated by a composite of the CBF regions was not significant.

This study adds to the literature linking MVRFs and brain health. An autopsy study showed that individuals with more severe diabetes were more likely to have reduced brain tissue volumes, including the hippocampus, compared to people without diabetes, whereas adults with prediabetes did not exhibit brain changes relative to controls (Schneider et al., 2017). Hippocampal volume was almost exclusively found to differ between people with and without diabetes, as determined by voxel-based morphometry MRI analyses (Gold et al., 2007); however, that diabetes group also had higher BMI, higher serum triglycerides, and lower serum HDL concentrations compared to...
controls (Gold et al., 2007). The vast majority of participants in the current study did not have diabetes (i.e., 97%). Thus, the present results of reduced CBF among those with increased MVRFs suggest that previous anatomical findings may underestimate the effect of MVRFs on the brain. The PLS latent variable implicated numerous ROIs that spanned all four lobes of the brain and included subcortical gray matter. The regions identified serve numerous brain functions, but collectively could be viewed as regions involved in neurodegeneration. Discussion on the specific MVRFs in relation to CBF are to follow; however, we speculate that MVRFs may induce changes in CBF more broadly than, and earlier than, neuroanatomical decline.

The current study focused primarily on gray matter CBF. White matter CBF accounted for a select number of ROIs, however, and is of interest as evidence points to neuropathological white matter changes and a pattern of reduced CBF from cortical gray to periventricular white matter (Tomimoto et al., 2003)(Makedonov, Black, & MacIntosh, 2013). Thus, further investigation on the physiological imaging of white matter is warranted, as newer approaches with background suppression and segmented 3D acquisition can provide the required sensitivity and spatial resolution (van Gelderen, de Zwart, & Duyn, 2008; Vidorreta et al., 2012).

The PLS identified regions where CBF contributed significantly to the latent variable. One previous report suggested that lower CBF among adults with type 2 diabetes, compared to controls, was mostly confined to temporal and parietal-occipital regions (Last et al., 2007). In contrast, CBF decrements were observed, in all lobes in the current study. Some of the pertinent brain regions, often implicated in functional neuroimaging studies of neurodegeneration, that were identified in this study include the angular gyrus, cuneus, basal ganglia structures, hippocampus, insula, cingulate regions, among others. The large number of CBF ROI detected was not the result of an ASL signal quality bias, that is, radio frequency coil-loading bias, as the ratio of whole brain CBF between ASL and phase contrast angiography was not influenced by between-subject differences in BMI. Instead, the multivariate PLS proved to be a robust method of integrating the between-subject variance and ascertain a feature in the data that were consistent across the many CBF regions. In addition, to address the potential partial volume effects, CBF estimates were first down sampled to participant specific regions of interest to account for regional tissue difference. Second, CBF estimates were adjusted prior to the PLS analyses by total brain volume.

Neither systolic nor diastolic blood pressure contributed to the latent variables in the PLS models. There are two important points to make regarding these findings. First, a second latent variable from the PLS model clearly reflected blood pressure, but it explained only a small amount of variance (i.e., 9.3%) and it was not significantly related to CBF. The lack of blood pressure influence may appear paradoxical; however, other cohorts, that is, men with coronary artery disease and adults in their 80s, also report no associations between blood pressure and CBF features (Foster-Dingley et al., 2015; MacIntosh et al., 2015). Second, treatment for hypertension may have a confounding effect. To address this, we considered sensitivity analyses in subgroups based on treatment for a history of hypertension. Although the subgroup without hypertension showed a qualitatively similar pattern, the strength of the partial correlations was more modest, and the latent variable did not reach significance. Among those with a history of hypertension, the effects of the other MVRFs on CBF were larger and significant. This result on midlife CBF extends previous neuroanatomical findings that document additive effects of these MVRFs on atrophy in older people (Tchistiakova & MacIntosh, 2016). It might be considered that although treatment for hypertension can bring many people with a history of hypertension into normal blood pressure ranges, it may not correct other abnormalities in vessel function that confer vulnerability to other MVRFs. Further investigation is warranting, however, as we did not examine the influence that specific hypertension medications or adherence may have on the current results.

Hyperinsulinemia featured prominently in the PLS latent variable. Although particular underlying mechanisms remain hypothetical, one theory suggests that insulin resistance might reduce transport of insulin into the brain, leading to a paradoxical cerebral insulin deficiency that tends to target temporal and frontal brain regions where insulin receptors are expressed (Craft, 2005). Insulin may be involved in clearance of the beta-amyloid protein, and modulate inflammatory cytokine signaling (Craft, 2005; Watson et al., 2003), which could alter brain structure, function, and CBF. Hyperinsulinemia was closely related to hyperglycemia, which in animal models can be harmful during hypoxia-ischemia conditions (Chang et al., 1998) and which can affect endothelial function through increased oxidative stress, reduced nitric oxide availability and increased endothelin-1 mediated vasoconstriction, among other potential mechanisms (Kalani, 2008; Monnier et al., 2006).

Two obesity metrics, BMI and waist circumference, contributed to the significant latent variable, adding to previous brain imaging obesity findings (Debette et al., 2010; Ho et al., 2010; Raji et al., 2010). While these measures were chosen based on established clinical relevance, they cannot speak directly to adiposity or fat distribution pattern (e.g., visceral vs. subcutaneous), and more precise obesity metrics might be useful in future studies to better inform underlying mechanisms.

The PLS findings implicated triglycerides and HDL variables, which are influenced by eating habits, smoking, sedentary lifestyle, and obesity. Our findings appear at odds with one study that reported that these variables did not influence cognition over a 7-year period among non-demented adults living in their 70s (Reitz, Luchsinger, Tang, Manly, & Mayeux, 2005); however, a more recent study found that high triglycerides in midlife were associated with increased risk of AD markers, that is, protein concentrations in cerebrospinal fluid, and evidence of amyloid in tissue during 20 year follow-up imaging (Någga et al., 2018). The findings in to, lend further support to the notion that midlife can be a crucial juncture at which MVRFs set the stage for later cognitive decline.

In our sample of largely nondiabetic participants, we observed a direct association between MVRFs and memory performance, which concurs with work by Gold et al., who found that short and long delayed recall were affected in diabetes (Gold et al., 2007). We, however,
did not find evidence that CBF mediated the relationship between MVRFs and memory performance in midlife that was described previously (Yaffe et al., 2014). Notably, the mean of the PLS-defined regional CBF values was not associated with memory performance. It is possible that averaging CBF across the ROIs failed to account for regional differences that may be important sources of heterogeneity between participants. Another possibility is the potential of ceiling effects in the CBF or RAVLT measures, as this group included cognitively intact 50-year-old adults. The results do not preclude longitudinal relationships, or cerebrovascular reactivity, which was not assessed here, as a potential mediator (Albanese et al., 2017; Tchistiakova & MacIntosh, 2016).

The current study is limited to cross-sectional observations; therefore, additional work is required to understand whether CBF predicts future clinical cognitive outcomes. The narrow age range in this study is strength; however, this along with the cross-sectional data preclude our ability to test for an age-effect in relationships between MVRFs, CBF, and cognitive changes (Barrett-Connor, Edelstein, Corey-Bloom, & Wiederholt, 1996). We are also not able to address the potential influence of large artery vascular disease, such as steno-occlusive disease, as angiography data were not collected; thus, this could be a source of between-subject differences in CBF. As for the arteries in the neck, the phase contrast angiography was prescribed the same physical distance below the ASL imaging volume. Our choice of the upper velocity cut-off that was comparable to previous work (Khan et al., 2017), but could have introduced some bias in the phase contrast CBF quantification. The phase contrast images were therefore visually inspected to ensure that all four neck arteries were visible in each participant in this analysis. Lastly, amyloid and tau biomarkers were not available to exclude potential early stage AD.

Adults in midlife with increased MVRFs, decreased CBF, and poor memory performance might be viewed as an important target population for preventative interventions. Therefore, understanding cognitive performance in this cohort may be of paramount clinical importance. Additional work will be needed to better characterize neuroendocrine changes that affect trajectories of CBF and cognitive performance in middle-aged adults with and without early neurodegenerative changes (Ishii & Iademola, 2015).

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DATA AVAILABILITY STATEMENT

Data in this study are from a sub-sample of black and white men and women who participated in the community-based Coronary Artery Risk Development in Young Adults (CARDIA) study, examined at year-25. CARDIA is a longitudinal study of the development and determinants of cardiovascular disease in 5115 young adults who were aged 18–30 years at baseline in 1985–1986.

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