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Association of Cardiovascular and Alzheimer's Disease Risk Factors with Intracranial Arterial Blood Flow in Whites and African Americans

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Abstract

Background: Alzheimer's disease (AD) has a higher prevalence among African Americans. Targeting cardiovascular and metabolic risk factors may be potential mechanisms to modify AD risk and address racial/ethnic disparities in AD dementia.

Objective: This study investigated relationships among cardiovascular and metabolic risk factors, *APOE* genotype, AD biomarkers, and intracranial arterial blood flow in Whites and African Americans enriched for AD risk.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

Methods: 399 cognitively unimpaired adults from the Wisconsin Alzheimer's Disease Research Center completed physical and neuroimaging examinations. A 4D Flow MRI sequence (phase-contrast vastly under sampled isotropic projection imaging) measured intracranial arterial flow in the Circle of Willis. Linear mixed-effects regression models estimated relationships between risk factors and intracranial arterial flow and tested interactions with racial group, *APOE* genotype, and AD biomarkers, with separate models per risk factor.

Results: Higher fasting glucose was associated with lower intracranial arterial flow; no additional relationships between flow and risk factors were observed. Main effects of racial group were observed, without an interaction, indicating lower flow in African Americans compared to Whites. In race-stratified analyses, higher glucose and triglycerides were associated with lower flow for African Americans, but not for Whites. No main effects or interactions among risk factors, *APOE* or AD biomarkers, and flow were observed.

Conclusion: Elevated fasting glucose and triglycerides were associated with lower intracranial arterial flow; these relationships were more prominent in African Americans. Targeting metabolic risk factors may impact intracranial arterial health. Additional research is needed to determine if this will impact disparities in dementia prevalence.

Keywords

Alzheimer Disease; cerebrovascular circulation; risk factors; African Americans; metabolic syndrome; glucose; Apolipoprotein E4; Aging; neuroimaging

INTRODUCTION

Alzheimer's disease is the most common cause of dementia among older adults (≥ 60 years old), affecting more than 5.3 million people in the United States [1]. The prevalence of Alzheimer's disease is estimated to triple over the next 30 years [2], with 106 million cases of Alzheimer's disease expected worldwide. However, despite the urgency to identify potential Alzheimer's disease modifying agents, there are still limited therapeutic options [2, 3]. There is growing evidence that the etiology of Alzheimer's disease reflects complex interactions between age, genetic risk factors, health behavior (*e.g.* physical activity, diet, tobacco use), environmental factors, cardiovascular and metabolic risk factors [4]. Modifiable cardiovascular and metabolic risk factors (*e.g.*, hypertension, dyslipidemia, obesity, diabetes mellitus, insulin resistance) present at middle age significantly increase risk for cognitive impairment, vascular dementia, and Alzheimer's Disease [4, 5]. Therefore, the American Heart Association and American Stroke Association recommend that cardiovascular and metabolic risk factors be potential major targets for the prevention of dementia [6]. Worldwide, it is estimated that approximately 23 million cases of dementia due to Alzheimer's disease could be avoided by the year 2050, if the onset of disease is delayed by 2 years with preventive interventions [6].

Although vascular risk factors may be associated with markers of Alzheimer's disease pathophysiology (*e.g.*, beta-amyloid [A β] burden) in midlife [7], the cerebrovascular mechanisms by which vascular disease increases risk for later-life Alzheimer's disease dementia remain unknown. Changes in vasculature that become more common with

advanced age, such as atherosclerosis and vessel stiffening, can disrupt delivery of essential nutrients to neurons via blood flow. Prior studies using a four-dimensional (4D) flow MRI technique to quantify intracranial arterial health have observed lower intracranial arterial blood flow in individuals with dementia and mild cognitive impairment [8–11]. Additionally, associations between lower intracranial arterial blood flow, elevated atrophy of brain tissue, and lower A β ₄₂ in the cerebrospinal fluid (CSF) were noted in a sample of cognitively healthy and cognitively impaired adults [12]. Our prior studies also showed that higher overall vascular risk burden was associated with lower blood flow in middle cerebral arteries (MCA) and internal carotid arteries (ICA) [13]; higher insulin resistance was also associated with lower ICA flow [14].

However, there is a growing body of evidence that African Americans have a greater risk of Alzheimer's disease compared to the non-Hispanic white population [15–19]. The prevalence of cognitive impairment or Alzheimer's disease is two to three times higher among older African Americans than in older non-Hispanic whites [16–20]. Per U.S. data, African Americans have a greater prevalence of vascular risk factors and cerebrovascular disease. Unfortunately, due to limited recruitment of African Americans within Alzheimer's disease studies, there is minimal understanding of the pathways linking risk factors to Alzheimer's disease across race/ethnicities [20].

Overall, prior results suggest that vascular risk factors may be associated with lower intracranial arterial blood flow in individuals at-risk for or diagnosed with cognitive impairment. However, more information is needed on the unique contributions of individual cardiovascular risk factors to intracranial arterial blood flow in adults at-risk for Alzheimer's disease. Additional research is also needed to determine if genetic risk or presence of Alzheimer's disease pathophysiology moderates the relationship between vascular risk factors and intracranial flow, and if relationships vary in populations with elevated vascular risk such as African Americans. Therefore, the aims of this study were to: 1) investigate the unique relationships between modifiable cardiovascular risk factors and intracranial arterial blood flow (as measured via 4D-Flow MRI), in a racially diverse cognitively unimpaired late middle-aged population, 2) examine if increased genetic risk for Alzheimer's disease (Apolipoprotein E [APOE] ϵ 4 carrier status) or biomarkers of Alzheimer's disease (cerebrospinal fluid [CSF] beta-amyloid and tau, MRI hippocampal volume and atrophy) moderate the relationships between cardiovascular risk factors and intracranial arterial blood flow, and 3) determine if relationships between cardiovascular risk factors and intracranial arterial blood flow differ in African Americans compared to non-Hispanic Whites.

MATERIALS AND METHODS

Participants

This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board and the Wisconsin Alzheimer's Disease Research Center (ADRC). Participants included middle-aged and older adults enrolled in the Alzheimer's Disease Research Center (ADRC) Clinical Core whose risk for Alzheimer's disease was enriched due to a parental history of dementia. Participants were classified as cognitively unimpaired (*e.g.*, no evidence of mild cognitive impairment or dementia) at their baseline

study visit by consensus conference panel based on the National Institute on Aging – Alzheimer’s Association (NIA-AA) criteria [21,22]. Enrolled participants who self-identified as African American or non-Hispanic White as primary race/ethnicity and completed neuroimaging exams were included in this analysis.

Neuroimaging Data Acquisition

MRI scans were completed on a clinical 3T scanner (Discovery MR750, GE Healthcare, Waukesha, WI) using either a 32-channel (Nova Medical) or 8-channel head coil (Excite HD Brain Coil; GE Healthcare). All participants were instructed to abstain from food, tobacco, and caffeine at least four hours prior to the MRI scan. Phase-contrast vastly under sampled isotropic projection imaging (PC VIPR), a 4D flow MRI technique, which simultaneously captures vessel anatomy with dynamic velocity vector data allowing for detailed hemodynamic analysis, was used to acquire intracranial arterial blood flow [23–25]. Scan parameters for the PC VIPR acquisition were as detailed: $v_{enc} = 80$ cm/s, imaging volume = $22 \times 22 \times 10$ cm³, acquired isotropic spatial resolution = $(0.7 \text{ mm})^3$, TR (repetition time)/TE(echo time)=7.4/2.7ms, flip angle $\alpha=10^\circ$, bandwidth = 83.3KHz, 14,000 projection angles, scan time ~ 7 min, retrospective cardiac gating reconstructed into 20 cardiac phases with temporal interpolation [26]. A T1-weighted structural scan (BRAVO) was acquired axially using the following imaging parameters: 3D fast spoiled gradient echo sequence, inversion time = 450 ms; TR/TE = 8.1/3.2 ms; flip angle = 12° ; acquisition matrix = 256×256 ; field of view (FOV) = 256×256 mm²; and slice thickness = 1.0 mm.

Intracranial arterial blood flow quantification

Intracranial arterial 4D-flow data were processed using an in-house Matlab (The Mathworks; Natick, MA) based application termed the Centerline Tool, which allows for semi-automated segmentation and quantification of the intracranial arteries and veins [27]. Compared to manual segmentation of the cerebrovasculature, which requires significant time and user input, analysis using the centerline algorithm is faster and more reproducible. The internal carotid arteries (ICA) were measured in two locations, one superior position (approximately 7 mm [10 centerline points] below the posterior genu) and one inferior position (approximately 7 mm [10 centerline points] below the straight horizontal segment). The middle cerebral arteries (MCA) were measured approximately 5 mm (7 centerline points) from the juncture of the ICA and the MCA. The basilar artery was measured 5 mm (7 centerline points) from its origin from the vertebral arteries. These measurement locations were determined in consultation with a senior neuroradiologist (PT). All measurement locations were identified by experienced raters and then reviewed by a second rater before use. Experienced raters had to demonstrate an inter-rater reliability (intra-class correlation, random effects, compared with an average of the two most experienced raters) at each location greater than 0.9 for their measurements to be considered and reviewed by a second rater.

Cardiovascular and metabolic risk factors

The selection of cardiovascular and metabolic risk factors was based upon prior research by the Wisconsin Alzheimer’s Disease Research Center [12, 14], U.S. guidelines and statements on cardiovascular and cerebrovascular risk, and prior observational and

epidemiological studies on vascular risk, cognitive impairment, vascular dementia, and Alzheimer's Disease [6, 28, 29, 30]. Risk factors included fasting total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), fasting glucose, waist circumference, body mass index (BMI), systolic and diastolic blood pressure, cigarette tobacco use (current/former smoker vs. never smoker), cigarette tobacco exposure (total years smoked multiplied by the range of cigarettes/packs smoked daily [1 cigarette – <1/2 pack, 1/2 pack – <1 pack, 1 pack – <1.5 packs, 1.5 packs – <2 packs, or 2 packs]), and a composite vascular risk score (the ACC/AHA atherosclerotic cardiovascular disease [ASCVD] 10-year risk score) [28]. Cardiovascular and metabolic risk factor data were acquired after a minimum 12-hour overnight fast, during the physical examination at the WADRC clinical core study visit, closest in time to the MRI scan date (mean $\approx$ 3 months difference between study visit and MRI scan).

DNA collection and APOE genotyping

DNA was extracted at the baseline study visit from whole blood samples using the 5 Prime PerfectPure™ DNA Blood Kit (Fisher Scientific Company, LLC, Pittsburgh, PA) or the Gentra Puregene Blood Kit (Qiagen N.V., Venlo, Netherlands). DNA concentrations were quantified using UV spectrophotometry (Synergy™ 2 Multi-Mode Microplate Reader, BioTek Instruments, Inc., Winooski, VT) or the Thermo Scientific™ NanoDrop™ One UV-Visible spectrophotometer. *APOE* genotyping was performed by LGC Genomics (Beverly, MA) using competitive allele-specific PCR based KASP™ genotyping assays.

Beta-amyloid, tau, and neurodegeneration biomarkers

Cerebrospinal fluid (CSF) data were available for $n=183$ participants in the sample, who had complete data in other covariates. CSF was collected in the morning after a minimum 12-hour fast. A Sprotte spinal needle was used to extract 22 mL of CSF from the L3-L4 or L4-L5 vertebral interspace via gentle extraction into polypropylene syringes. Within 30 minutes of collection, the CSF was combined, gently mixed, centrifuged to remove red blood cells or other debris, aliquoted into 0.5-mL polypropylene tubes, and stored at -80 degrees Celsius. Samples were analyzed at the Clinical Neurochemistry Laboratory at the Sahlgrenska Academy of the University of Gothenburg, Sweden, for $A\beta_{1-40}$ and $A\beta_{1-42}$ using commercially available enzyme-linked immunosorbent assay methods (INNOTEST assays; Fujirebio, Ghent, Belgium; Triplex assays, MSD Human $A\beta$ peptide ultrasensitive kit; Meso Scale Discovery, Gaithersburg, MD). An $A\beta_{42}$ value of >471.54 pg/mL or an $A\beta_{42}/A\beta_{40}$ ratio of >0.09 was used to define elevated beta-amyloid ($A\beta$). A p-tau value >59.5 or t-tau value >461.26 was used to define elevated tau based on prior receiver operating characteristic analyses showing these values best discriminated cognitively healthy adults from individuals with dementia [31]. Using these thresholds, a CSF biomarker group variable with 4 levels ($A\beta-/Tau-$, $A\beta+/Tau-$, $A\beta-/Tau+$, $A\beta+/Tau+$) was created.

The T1-weighted volume was segmented into tissue classes using the updated segmentation feature in Statistical Parametric Mapping version 12 (SPM12, www.fil.ion.ucl.ac.uk/spm). Total intracranial volume (ICV; mm^3) was derived from the sum of the major tissue class volumes (gray and white matter and CSF volume). Global atrophy was quantified as CSF

volume divided by gray matter volume plus white matter volume. Hippocampal volume (mm^3) was calculated using the FMRIB Software Library FIRST tool (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>), a model-based segmentation/registration tool. Volumes for left and right hippocampus were summed to compute bilateral hippocampal volume. Bilateral hippocampal volume was divided by total ICV and this proportion value (hippocampal volume/ICV) was included in models [32].

Statistical analyses

Sample characteristics were compared across racial strata using Fisher's exact test for categorical or binary covariates, and Mann-Whitney U test for continuous items.

Linear mixed effects models were used to examine adjusted relationships between the risk factors and intracranial arterial flow. All models included fixed effects of age at MRI scan, sex (male/female), years of education, genetic risk for late-onset Alzheimer's disease (*APOE* $\epsilon 4$ carrier status), antihypertensive medication use, MR coil type (8- or 32-channel), vessel type (basilar, left and right MCA, left and right inferior and superior ICA), and two random intercepts: one for subject, and a second for vessel group nested within subject (ICA vs. non-ICA grouping). Diabetes mellitus was not included in all models due to collinearity with other risk factors (e.g., fasting glucose). The outcome variable of each model was the vessel specific intracranial arterial flow. Due to the concern of collinearity among the 13 risk factors of interests, separate models were run for each cardiovascular risk factor included as a covariate in the model, instead of including all 13 risk factors in the same model. The model described above, with a risk factor covariate included, was used to examine relationships between the risk factors and flow and represent the base models. There was reasonable concern that the effect of risk factor on flow might be vessel specific. Therefore, an interaction between the risk factor and vessel type was examined in these 13 models; however, Likelihood Ratio Tests did not indicate sufficient evidence to include these interactions in the base models.

In addition to the base models, several moderators of the risk factor / intracranial arterial flow were examined. Moderation by *APOE* $\epsilon 4$ carrier status was examined by including an interaction of *APOE* $\epsilon 4$ status and the risk factor to the base model. Moderation by Alzheimer's disease biomarkers was examined by adding a main effect of the biomarker, and its interaction with the risk factor, to the base model. As with the risk factors, concern of multicollinearity was such that only one of the three Alzheimer's disease biomarkers (CSF biomarker group, global atrophy, or hippocampal volume/ICV) was included in the model at a time. Due to the few participants who had both CSF and fasting glucose data available, no model for the CSF group moderation of fasting glucose could be performed. For most models, $n=183$ participants were included in analyses involving CSF and $n=375$ participants were included in analyses involving structural volume. Specific sample sizes for each of the models including the interaction of Alzheimer's disease biomarker x vascular risk factor are presented in the Supplemental Table.

Moderation by racial group was examined in two ways. First, by inclusion of a main effect of race, and its interaction with the risk factor, to the base model. Models with only the race main effect (no interaction) were also examined, as it is well known that African Americans

are typically at higher risk for many of the risk factors examined, compared to non-Hispanic Whites [33]. Second, by fitting race-specific models, as it is known that at least some covariates in the model (*e.g.* *APOE* $\epsilon 4$ carrier status) may not represent the same effect in both racial groups [34].

Asymptotic properties of fixed effects estimates were used to calculate p-values by Wald tests. Likelihood ratio tests were used to assess significant interactions with more than 1 degree of freedom (*i.e.*, CSF group interactions), and for omnibus tests (*e.g.* race and its interaction with a risk factor both being in a model). The False Discovery Rate (FDR) correction was applied across the 13 different risk factor models using the Benjamini-Hochberg method at an FDR control of 5%. For items with the same interpretation across models (*e.g.* age main effect, sex main effect, race main effect, etc.) no FDR correction was performed. Statistical significance was assessed at $\alpha = 0.05$ level.

All analyses were performed using R 3.5.1 [35]. Linear mixed effects were fitted using restricted maximum likelihood with ‘lmer()’ in the ‘lme4’ package [36]; for likelihood ratio tests, models were fit using maximum likelihood. Confidence intervals on figures were produced using the percentile method on parametric bootstrapping of the fitted model over 2000 iterations. Use of the vessel group random effect was necessary to alleviate a U-shaped trend in residuals, where halves of the U corresponded to the two vessel groups specified. With the vessel group random effect included, there were no major concerns for non-normal residuals, residuals trends, outliers, non-normal random effects, or correlation between random effects and residuals.

RESULTS

Sample characteristics

Summary characteristics are displayed in Table 1. On average, participants ($n=399$; $n=332$ Whites and $n=67$ African Americans) were late middle-aged (mean age = 62), highly educated (mean education = 16 years), and two-thirds were female (66%). There were no significant demographic differences between whites and African American participants. However, African Americans were generally more likely to have higher number of prevalent cardiovascular risk factors. African Americans had higher rates of diabetes mellitus. Of the 25 African Americans with diabetes mellitus, 24 had type 2 diabetes mellitus. Of the 31 White participants with diabetes mellitus, 25 had Type 2 diabetes mellitus.

Relationships among vascular risk factors and intracranial arterial flow

Statistical parameters are displayed in Table 2. Covariates of age, sex, vessel, and head coil were significantly associated with intracranial arterial flow in most models. In contrast, covariates of education, antihypertensive medication use, and *APOE* genotype were non-significant in all models. When risk factor *p*-values were FDR-adjusted, a significant relationship was observed between higher fasting glucose and lower intracranial arterial flow ($\beta = -0.004$ mL/min per mg/dL, $p < 0.001$); see Figure 1, top center panel. Without FDR-adjustment, a relationship was also observed between higher diastolic blood pressure and lower intracranial arterial flow (see Figure 1, top left panel). No relationships between the

remaining vascular risk factors and intracranial arterial flow were observed when p -values were unadjusted (remaining p 's > .13) or FDR-adjusted (remaining p 's > .21).

Effect of APOE genotype and Alzheimer's disease biomarkers on risk factor-flow relationships

When interaction p -values were FDR-adjusted, no significant interactions between *APOE* genotype x vascular risk factors on intracranial arterial blood flow were observed. For the associated unadjusted p -values, interaction terms of *APOE* genotype x total cholesterol ($p=.04$), *APOE* genotype x HDL-c ($p=.01$), *APOE* genotype x LDL-c ($p=.04$), and *APOE* genotype x triglycerides ($p=.006$) were significantly associated with intracranial arterial flow. No significant interactions between vascular risk factors and Alzheimer's disease biomarkers (CSF biomarker group, hippocampal volume/ICV, global atrophy) or main effects of Alzheimer's disease biomarkers on intracranial arterial blood flow were observed when p -values were unadjusted or FDR-adjusted.

Effect of racial group on risk factor-flow relationships

No interactions between vascular risk factors and race were observed when p -values were unadjusted or FDR-adjusted. With these interactions removed from the models, significant main effects of race on intracranial arterial blood flow indicated lower flow among African American participants compared to Whites (average $\beta=-0.308$ mL/min per mg/dL, all $p<0.001$); see Table 3. In race-stratified models (see Table 2), there were no significant relationships between vascular risk factors and intracranial arterial flow in FDR-adjusted models for White participants. For African American participants, a significant relationship between higher glucose and triglycerides and lower intracranial arterial flow was observed in FDR-adjusted models (glucose $\beta=-0.003$ mL/min per mg/dL, $p=0.006$; triglycerides $\beta=-0.002$ mL/min per mg/dL, $p=0.003$; see Figure 1, bottom panel).

DISCUSSION

In this middle-aged and older adult sample of 399 cognitively healthy adults enriched for Alzheimer's disease risk, we observed that elevated fasting glucose was associated with lower intracranial arterial blood flow. A weaker relationship (observed in individual model p -values >0.05 after FDR correction, but <0.05 before correction) was observed between elevated diastolic blood pressure and lower intracranial arterial flow; no significant relationships were observed between intracranial arterial blood flow and other cardiovascular or metabolic risk factors examined including systolic blood pressure, obesity (BMI, waist circumference, waist-to-hip ratio), lipids (total cholesterol, HDL-c, LDL-c, triglycerides), tobacco use, or composite vascular risk burden.

Interactions between racial group x risk factors on intracranial arterial blood flow were non-significant. When the interaction term was removed from all models, the main effect of race was significantly associated with intracranial arterial flow across all risk factor models. African American participants demonstrated lower intracranial arterial blood flow compared to Whites. When relationships between risk factors and flow were examined within racial groups separately, we observed significant relationships among elevated fasting glucose and

triglycerides and lower intracranial arterial blood flow in the African Americans that survived FDR-correction, even with the relatively small sample size of the strata. These relationships did not remain statistically significant in the White participants after FDR-correction despite the larger sample size in that group compared to the African American strata. These findings suggest that the relationships observed among metabolic risk factors and intracranial arterial blood flow may be driven by the African American participants, who have on average higher rates of risk factors, and that these relationships may be race-specific.

Metabolic syndrome, defined as a clustering of at least three of the five conditions: elevated triglycerides, low high-density lipoprotein cholesterol (HDL-c), elevated blood pressure (hypertension), elevated fasting glucose, and abdominal obesity (elevated waist circumference) [37], has a higher prevalence among African Americans compared to non-Hispanic Whites and is an important risk factor for diabetes mellitus [38], cardiovascular disease [39] and cerebrovascular disease, including stroke and Alzheimer's disease [40]; although the exact mechanisms are unknown. There is growing data that abnormalities in essential fatty acid metabolism, alterations in lipid metabolism, insulin resistance and abnormal leptin signaling may support the pathological association between metabolic syndrome and cerebrovascular disorders ("metabolic-cognitive syndrome") [40]. In a small study of racially/ethnically diverse middle-aged U.S. adults (n=83, 40–60 years old) without cognitive impairment or prior cardiovascular or cerebrovascular events, a greater number of metabolic risk factors (per the metabolic syndrome score, MetS score) was associated with lower cerebrovascular conductance within the middle cerebral artery [41].

Furthermore, some prior studies report associations between elevated markers of cerebrovascular dysfunction, such as arterial stiffness and/or reduced cerebral blood flow, and elevated dementia-related pathology (e.g., beta-amyloid deposition [42, 43]); however, others have not observed direct relationships among cerebrovascular dysfunction and Alzheimer's disease biomarkers, but have rather found interactions among them on cognitive decline [44]. In our prior work, we observed lower internal carotid artery flow in a small sample of older adults with mild cognitive impairment who had elevated brain markers of beta-amyloid. In contrast, in this larger racially diverse cognitively unimpaired sample, we did not observe relationships among markers of Alzheimer's disease or dementia-related biomarkers (e.g., beta-amyloid, tau, hippocampal volume, global brain atrophy) and intracranial arterial blood flow; nor did we observe a moderation of these markers on the relationships between risk factors and flow. We also did not observe a relationship between genetic risk for late-onset Alzheimer's disease (*APOE* ϵ 4 carriage) and intracranial arterial blood flow; however, weak relationships (observed in individual model p-values that did not survive FDR-correction) between *APOE* genotype x total cholesterol, HDL-c, LDL-c, and triglycerides suggest possible differential relationships between lipids and intracranial blood flow in *APOE* ϵ 4 vs. non- ϵ 4 carriers. Prior literature suggests that genetic risk for late-onset Alzheimer's disease may be associated with cerebrovascular dysfunction by reducing cerebral blood flow, modifying coupling between cerebral blood flow and neuronal signaling, and increasing blood-brain barrier leakiness, cerebral amyloid angiopathy, hemorrhages, and transport of nutrients and toxins [45].

There are several limitations to the current study that should be considered including generalizability of the study findings to those at elevated risk for Alzheimer's disease, differences in vascular risk factors among African Americans and Whites and smaller sample of participants with CSF data available (particularly in the African American sample). MRI hardware changes (e.g., head coil) occurred during the course of the study and may increase noise in the outcome variable; however coil type was included in all models to minimize overall measurement variance. Additionally, although antihypertensive medication was included in the analysis, we were unable to evaluate the effect of diabetes medication on biomarker levels and vascular outcomes, and thus various levels of certain blood biomarkers might be a partial proxy for medication use as well. The complex nature of ASCVD scores along with use of covariates that are needed to calculate the score (age, sex, race, etc.) can make interpretation of the effect of ASCVD and its moderation/mediation difficult to interpret. Despite the limitations, this study suggests that elevated fasting glucose may be particularly deleterious for intracranial arterial vessel health; this may be a target for improving cerebral blood flow and reducing risk for cognitive decline. Our findings highlight the need to further examine metabolic risk factors, particularly in African Americans and other under-represented populations. Future directions include examination of additional markers of cerebrovascular health not included here such as white matter hyperintensities, arterial stiffness, and micro bleeds, as well as examining associations between cumulative vascular/metabolic risk factor burden, Alzheimer's disease biomarkers, and cerebrovascular health in longitudinal models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1 (color for online version).

Estimated relationships among intracranial arterial blood flow and diastolic blood pressure (left), fasting glucose (center), and triglycerides (right) in the total sample of 399 participants (top row) and in separate models for African Americans (red; $n=67$) and Whites (blue; $n=332$) (bottom row). All non-risk factor covariates were set to their median value for continuous covariates, and their mode for binary or categorical covariates.

Figure 1 (grey-scale for print version).

Relationships among intracranial arterial blood flow and diastolic blood pressure (left), fasting glucose (center), and triglycerides (right) in the total sample of 399 participants (top row) and in separate models for African Americans (darker grey; $n=67$) and Whites ($n=332$; light grey) (bottom row). All non-risk factor covariates were set to their median value for continuous covariates, and their mode for binary or categorical covariates.

TABLE 1.

Sample characteristics

	Total	White	African American	<i>p</i>
N	399	332	67	
Age, years	61.87 (8.65)	61.60 (8.71)	63.23 (8.28)	0.123
Female (%)	262 (65.7)	216 (65.1)	46 (68.7)	0.672
APOE e4 carrier (%)	137 (34.3)	119 (35.8)	18 (26.9)	0.204
Education, years	16.14 (2.60)	16.20 (2.61)	15.88 (2.56)	0.325
Antihypertensive Medication Use (%)	121 (30.5)	81 (24.4)	40 (61.5)	<0.001
Diabetes mellitus (%)	56 (14.0)	31 (9.3)	25 (37.3)	<0.001
ASCVD 10-year risk score	10.94 (12.92)	9.65 (12.78)	17.62 (11.61)	<0.001
Systolic blood pressure, mmHg	128.29 (17.47)	125.93 (15.86)	139.96 (20.31)	<0.001
Diastolic blood pressure, mmHg	76.74 (9.15)	75.36 (8.68)	83.61 (8.31)	<0.001
Waist-to-hip ratio	0.91 (0.09)	0.90 (0.09)	0.94 (0.08)	0.001
Waist circumference, cm	96.93 (15.50)	95.06 (14.92)	106.20 (15.10)	<0.001
Body Mass Index, kg/m²	29.22 (5.98)	28.44 (5.62)	33.09 (6.24)	<0.001
LDL-c, mg/dL	113.45 (33.29)	114.61 (32.17)	107.45 (38.27)	0.225
HDL-c, mg/dL	62.09 (18.96)	62.99 (18.54)	57.51 (20.50)	0.029
Total Cholesterol , mg/dL	196.48 (37.97)	198.68 (37.16)	185.29 (40.31)	0.018
Triglycerides, mg/dL	111.80 (88.46)	110.54 (90.12)	118.18 (79.86)	0.443
Glucose, mg/dL	100.47 (29.36)	97.37 (22.30)	113.65 (47.27)	0.028
Current or former tobacco use (%)	145 (36.3)	108 (32.5)	37 (55.2)	0.001
Tobacco exposure, pack-years	12.67 (26.05)	10.74 (24.55)	22.22 (30.94)	<0.001
Hippocampal volume, mm³	7792.08 (891.03)	7883.15 (852.49)	7334.00 (944.93)	<0.001
Intracranial volume (ICV), mm³	1473.95 (148.24)	1481.63 (147.53)	1435.89 (146.91)	0.011
Hippocampal volume/ICV	0.53 (0.06)	0.53 (0.06)	0.51 (0.06)	0.009
Global atrophy	3.36 (0.91)	3.42 (0.88)	3.08 (1.01)	0.001
Cerebrospinal Fluid Group (%)				0.678
Biomarker negative	137 (71.0)	133 (70.7)	4 (80.0)	
Aβ+ and tau–	22 (11.4)	22 (11.7)	0 (0.0)	
Tau+ and Aβ–	16 (8.3)	16 (8.5)	0 (0.0)	
Aβ + and tau+	18 (9.3)	17 (9.0)	1 (20.0)	
MRI Head Coil Type (% 32-channel)	129 (32.3)	86 (25.9)	43 (64.2)	<0.001

Values are given as mean (standard deviation) unless otherwise specified; LDL-c (low-density lipoprotein cholesterol); HDL-c (high-density lipoprotein cholesterol); Aβ (Beta-amyloid); ASCVD (atherosclerotic cardiovascular disease); Global atrophy was calculated as CSF volume (mm³) divided by gray matter volume (mm³) plus white matter volume (mm³); Diabetes mellitus included 7 participants with Type I diabetes (1 African American, 6 White) and 49 participants with Type II diabetes (24 African American and 25 White).

Table 2.

Relationship between risk factor and intracranial arterial blood flow

Model		Total sample		White sample		African American sample	
	Risk Factor	N	Beta (SE)	N	Beta (SE)	N	Beta (SE)
1	ASCVD 10-year risk score	379	−0.004 (.003)	320	−0.0002 (.004)	59	−0.010 (.006)
2	Systolic blood pressure	381	−0.002 (.002)	321	0.0006 (.002)	60	−0.002 (.003)
3	Diastolic blood pressure	381	−0.006 (.003) *	321	−0.0032 (.003)	60	−0.004 (.006)
4	Waist circumference	381	−0.003 (.002)	321	0.0002 (.002)	60	−0.006 (.003)
5	Waist-to-Hip Ratio	381	−0.356 (.355)	321	0.0574 (.389)	60	−1.460 (.760)
6	Body Mass Index	381	−0.007 (.004)	321	0.0006 (.005)	60	−0.015 (.008) *
7	LDL-c	376	0.001 (.001)	318	−0.0001 (.001)	58	0.002 (.001)
8	HDL-c	379	0.001 (.002)	320	0.00001 (.002)	59	0.002 (.003)
9	Total cholesterol	379	0.0004 (.001)	320	−0.0001 (.001)	59	0.001 (.001)
10	Triglycerides	378	−0.0003 (.000)	319	0.00002 (.000)	59	−0.002 (.001) * ⁺
11	Glucose	277	−0.004 (.001) * ⁺	227	−0.0042 (.002) *	50	−0.003 (.001) * ⁺
12	Current or former smoker	381	0.013 (.055)	321	0.0819 (.063)	60	−0.045 (.100)
13	Tobacco exposure	135	0.001 (.001)	102	0.0011 (.002)	33	0.000 (.002)

Each linear mixed-effects regression model included fixed effects of age, sex, education, antihypertensive medication use, vessel (Left ICA, Right ICA, Left SICA, Right SICA, Left MCA, Right MCA, Basilar), head coil type (8-channel, 32-channel), and intercept random effects for person and vessel group (non-ICA or ICA). For total sample analyses, covariates of age, sex, vessel type, and head coil type were significantly associated with intracranial arterial flow in most models, whereas covariates of education, antihypertensive medication use, and *APOE* genotype were non-significant in all models.

ASCVD (atherosclerotic cardiovascular disease); LDL-c (low-density lipoprotein cholesterol); HDL-c (high-density lipoprotein cholesterol);

* p<.05 non-FDR-adjusted;

⁺ p<.05 FDR-adjusted

Table 3.

Relationship between racial group and intracranial arterial flow

Interaction of risk factor x racial group			Main effect of racial group after interaction term removed from models	
Model	Risk Factor	N	Beta (SE)	Beta (SE)
1	ASCVD 10-year risk score	379	0.005 (0.006)	−0.289 (0.080) [*]
2	Systolic blood pressure	381	−0.001 (0.004)	−0.305 (0.081) [*]
3	Diastolic blood pressure	381	0.000 (0.008)	−0.281 (0.081) [*]
4	Waist circumference	381	−0.006 (0.005)	−0.293 (0.079) [*]
5	Waist-to-Hip Ratio	381	−0.628 (0.900)	−0.3 (0.079) [*]
6	Body Mass Index	381	−0.015 (0.011)	−0.293 (0.080) [*]
7	LDL-c	376	0.001 (0.002)	−0.287 (0.080) [*]
8	HDL-c	379	0.001 (0.004)	−0.294 (0.079) [*]
9	Total cholesterol	379	0.000 (0.002)	−0.295 (0.079) [*]
10	Triglycerides	378	−0.002 (0.001) [*]	−0.293 (0.079) [*]
11	Glucose	277	0.002 (0.002)	−0.239 (0.096) [*]
12	Current or former smoker	381	−0.135 (0.143)	−0.319 (0.079) [*]
13	Tobacco exposure	135	0.000 (0.003)	−0.51 (0.113) [*]

Each linear mixed-effects regression model included fixed effects of age, sex, education, antihypertensive medication use, vessel (Left ICA, Right ICA, Left SICA, Right SICA, Left MCA, Right MCA, Basilar), head coil type (8-channel, 32-channel), and intercept random effects for person and vessel group (non-ICA or ICA).

ASCVD (atherosclerotic cardiovascular disease); LDL-c (low-density lipoprotein cholesterol); HDL-c (high-density lipoprotein cholesterol)

^{*} p<.05 non-FDR-adjusted