Title
Cerebral perfusion and amyloidosis in the oldest-old

Journal
Alzheimer's & Dementia, 20(12)

ISSN
1552-5260

Authors
Dutt, Shubir
Woodworth, Davis C
Sajjadi, S Ahmad
et al.

Publication Date
2024-12-01

DOI
10.1002/alz.14357

Peer reviewed

Received: 2 July 2024 | Revised: 17 September 2024 | Accepted: 1 October 2024

DOI: 10.1002/alz.14357

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

SHORT REPORT

Cerebral perfusion and amyloidosis in the oldest-old

Shubir Dutt[1,2] | **Davis C. Woodworth**[3,4] | **S. Ahmad Sajjadi**[3,4] | **Dana E. Greenia**[4] | **Charles DeCarli**[5] | **Claudia H. Kawas**[3,4,6] | **María M. Corrada**[3,4,7] | **Daniel A. Nation**[8,9]

[1]Department of Neurology, Memory and Aging Center, Weill Institute for Neurosciences, University of California, San Francisco, California, USA

[2]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, California, USA

[3]Department of Neurology, University of California, Irvine, California, USA

[4]Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, California, USA

[5]Department of Neurology, University of California, Davis, Sacramento, California, USA

[6]Department of Neurobiology and Behavior, University of California, Irvine, California, USA

[7]Department of Epidemiology and Biostatistics, University of California, Irvine, California, USA

[8]Leonard Davis School of Gerontology, University of Southern California, Los Angeles, California, USA

[9]Department of Physiology and Neuroscience, Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Correspondence
Daniel A. Nation, Leonard Davis School of Gerontology, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089, USA.
Email: danation@usc.edu

Funding information
National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD)/National Institute on Aging (NIA), Grant/Award Number: U24AG021886; National Institutes of Health, Grant/Award Numbers: R01AG064228, R01AG060049, R01AG082073, P01AG052350, P30AG066530, R01AG062706, R01AG021055, U19NS120384, P30AG072972, RF1AG054548, R56AG048642, R01AG075758

Abstract

INTRODUCTION: In a nested case–control study, we examined how cerebral perfusion relates to cognitive status and amyloid in the oldest-old (i.e., 90 years of age and older).

METHODS: Study participants included 113 dementia-free older adults (76 cognitively normal [CN]; 37 cognitively impaired, no dementia [CIND]) from *the 90+ Study* (mean age = 92.9, SD = 2.4). We quantified regional perfusion from arterial spin labeling-MRI (magnetic resonance imaging) and amyloid deposition from florbetapir-positron emission tomography (PET) in a region comprising the posterior cingulate and precuneus (PCC+PCu), and additionally quantified perfusion in other regions important for cognitive decline (medial temporal lobe, inferior parietal lobe, and orbitofrontal cortex).

RESULTS: Participants with CIND displayed lower perfusion in the PCC+PCu relative to participants who were CN, but there was no statistically significant difference between the groups in amyloid burden in this region. In addition, participants with CIND exhibited lower inferior parietal and higher orbitofrontal perfusion.

DISCUSSION: Cerebral perfusion is related to cognitive status in the oldest-old independent of amyloidosis.

KEYWORDS
aging, amyloid PET, arterial spin labeling, cerebral perfusion, cerebrovascular function, oldest-old

Highlights

- Cerebral perfusion and amyloid positron emission tomography (PET) were measured in older adults: 90 years of age and older.
- Perfusion but not amyloid differed between cognitively impaired and normal groups.
- Frontal and parietal regions linked to cognitive decline had altered perfusion.
- Perfusion is related to cognitive status in the oldest-old independent of amyloid.

1 | INTRODUCTION

Cerebrovascular contributions to cognitive aging processes and dementia risk represent a rapidly growing field in aging research. Vascular dysregulation, as represented by altered brain perfusion or cerebral blood flow (CBF), can predict future cognitive decline and dementia risk in cognitively normal individuals,[1–3] with some studies suggesting that early cerebrovascular abnormalities may trigger and exacerbate links between amyloid and tau in disease progression.[4,5] The "vascular hypothesis" positing neurodegeneration in Alzheimer's disease (AD) dementia as a downstream consequence of early neurovascular alterations implicates hypoperfusion as an early important event in neurodegenerative diseases.[6,7] This has been supported by larger population studies suggesting that cerebral hypoperfusion may precede abnormality of other well-established biomarkers of AD.[8] However, most of these studies focus on participants in midlife or earlier stages of aging (i.e., young-old), and less is known about how cerebrovascular function is impacted in the oldest-old (i.e., individuals 90 years of age and older), who represent the fastest growing portion of the population and are at the greatest risk for dementia.[9,10]

Neuroimaging studies among the oldest-old are relatively scarce, with very few studies examining perfusion changes specifically in this population.[11] The few perfusion studies in the oldest-old have focused on a younger age band (i.e., mean age of 85 years) and examined the relationship between perfusion and white matter disease, but did not more broadly characterize patterns of cerebral perfusion.[12,13] Prior studies of the oldest-old in *The 90+ Study* have reported unique vascular factors in this population, including a lower risk for dementia in those with hypertension.[14] In contrast, randomized trials in the young-old have shown that treatment of hypertension may improve brain perfusion, but this is understudied in the oldest-old.[15] Thus, a significant gap exists in concurrently studying cerebral perfusion and positron emission tomography (PET) –quantified amyloid deposition among the oldest-old.

We characterized patterns of cerebral perfusion in regions that experience age-related changes in CBF among dementia-free participants with and without cognitive impairment from *The 90+ Study*. We then compared, in the same anatomic region, cerebral perfusion and amyloid beta (Aβ) load as measured by florbetapir-PET between cognitively unimpaired and impaired individuals to better understand whether cognitive status is more closely associated with amyloid burden or cerebrovascular dysfunction.

2 | METHODS

2.1 | Participants

The present nested case–control study draws from participants in *The 90+ Study*, an ongoing longitudinal study of community-dwelling oldest-old adults designed to examine cognitive aging and dementia in the oldest-old.[16] Our study included individuals who completed (1) a pseudo-continuous arterial spin labeling (pCASL) magnetic resonance imaging (MRI) brain scan and (2) an amyloid PET scan. Study participants underwent comprehensive neurological examination and neuropsychological testing and were classified as cognitively normal (CN), cognitively impaired, no dementia (CIND), or dementia, only participants with a diagnosis of CN or CIND were included in the present study in order to highlight findings before dementia onset (see Section 2.2). After exclusion of eight participants with dementia and pCASL quality control exclusions (see Section 2.3), a total of 113 participants were included in primary analyses (see Figure 1 for a flow chart of inclusion/exclusion). An additional analysis was performed in a subset of 97 participants who had available apolipoprotein E (*APOE*) ε4 genotyping (See Section 2.5). In addition, we used demographic and medical history variables such as participant age at MRI scan, sex, education, and presence or absence of vascular risk factors (hypertension, stroke, heart disease, transient ischemic attack, and diabetes). All participants or their designated informants granted written informed consent for participation, and the research study was approved by the University of California Irvine Institutional Review Board.

2.2 | Cognitive status and medical history

Cognitive status was assessed by formal structured neurological, cognitive, and functional exams (Clinical Dementia Rating [CDR] scale, Functional Activities Questionnaire [FAQ], Mini-Mental State Examination [MMSE], and modified MMSE [3MS]).[17,18] Participants were diagnosed with dementia if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major neurocognitive disorder; eight participants were diagnosed with dementia and excluded from the study. Participants were diagnosed with CIND if they had some cognitive impairment or functional loss but did not meet DSM-IV criteria for dementia. Participants were classified as CN if they had no cognitive or functional impairment.

History of vascular risk factors was self-reported by participants by responding "yes" or "no" to whether they had ever been diagnosed with hypertension, stroke, heart disease, transient ischemic attack, and diabetes.

2.3 | MRI acquisition and processing

All individuals were scanned on the same GE Discovery 750 W 3T scanner (General Electric Healthcare, Waukesha, WI). We acquired a pCASL scan, which implemented background suppression and a fast-spin echo with spiral readout that produced a volumetric three-dimensional (3D) acquisition.[19] The 3D slab was positioned at the base of the cerebellum. Scan parameters were as follows: post-labeling delay (PLD) of 2025 ms, a repetition time (TR) of 4852 ms, an echo time (TE) of 11 ms, a flip angle (FA) of 111^0, a voxel size of 2 mm × 2 mm × 4 mm, number of excitations (NEX) of 3, and 40 label-control pairs. The PLD was selected as more appropriate for this age group because of increased arterial transit times[20] and is the same as that used for the equivalent GE protocol in the Alzheimer's Disease Neuroimaging Initiative (ADNI) 3 protocol.[21] The scanner produced CBF images in mL/100 g/min, which were then used for further processing and analysis.[22] The protocol also included a high-resolution (1 mm isotropic) 3D T1-weighted inversion recovery fast-spoiled gradient recalled echo (3D T1w IR-FSPGR) sequence based on the ADNI3 protocol,[21] which was also used for processing of the CBF maps.

Scanner-derived CBF maps (n = 184) for each participant were first visually inspected by two independent raters for gross artifacts or distortions, resulting in 113 scans being included. CBF maps were warped to Montreal Neurological Institute (MNI) space and thresholded to a biologically plausible range of 10–150 mL/100 g/min.[23–26] A group-averaged whole brain gray matter (GM) mask derived from segmented T1 images (via Statistical Parametric Mapping 12 [SPM12]) was used to quantify whole brain GM CBF values.[27] GM masks from the automated anatomical atlas 3 (AAL3) atlas and Wake Forest Univeristy PickAtlas (WFUPickAtlas were applied to extract CBF values for individual regions of interest (ROIs).[28,29] We selected ROIs a priori from observed perfusion changes in younger-old populations including the precuneus, posterior cingulate, medial temporal lobe, orbitofrontal cortex, and inferior parietal lobe.[30–33] A combined posterior cingulate + precuneus region was calculated to mirror the ROI used in amyloid PET quantification (see Section 2.4). CBF in individual ROIs were normalized to whole brain GM CBF via division to correct for global perfusion.[31,34]

2.4 | Amyloid PET acquisition and processing

Participants underwent florbetapir-PET scanning (two 5-min frames after a 50-min delay following florbetapir F18 tracer injection) to quantify Aβ deposition.[35] Native PET images underwent quality control, realignment of frames, and alignment to standardized template space, followed by quantification of standard uptake value ratio (SUVR) values normalized to an eroded cerebral white matter mask. SUVR quantified in a statistically derived ROI comprising the posterior cingulate and precuneus (PCC+PCu) were most closely associated with cognitive status and provided robust separation of amyloid status at autopsy.[36–38] A threshold of 0.76 was used to denote Aβ-PET positivity also based on correspondence analysis in autopsy-confirmed cases.[36,37]

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional methods (e.g., PubMed) for studies on functional neuroimaging of cerebral blood flow across the lifespan and specifically within the oldest-old (i.e., 90 years of age and older) segment of the population. There are numerous studies on cerebral blood flow in the young-old but very few have studied perfusion in the oldest-old, and none have compared perfusion to amyloidosis in this age range.
2. **Interpretation**: We found that, among the oldest-old, cognitively impaired individuals had lower magnetic resonance imaging (MRI)–quantified cerebral perfusion than unimpaired individuals in an Alzheimer's disease (AD) risk region, but groups did not significantly differ in positron emission tomography (PET)–quantified amyloid deposition in the same region. Groups also differed in frontal and parietal perfusion.
3. **Future directions**: Future studies will further characterize cerebral perfusion in comparison to other biomarkers of aging and disease (e.g., tau) to better understand the protective factors against cognitive impairment in advanced age.

2.5 | APOE genotyping

DNA samples for *APOE* genotyping were acquired from either a cheek swab or a blood draw. Participants were classified as *APOE* ε4 carriers if they possessed at least one ε4 allele (i.e., ε2/ε4, ε3/ε4, ε4/ε4) and were noncarriers if they did not possess an ε4 allele.

2.6 | Statistical analyses

Analysis of variance (ANOVA) and chi-square tests examined group differences in continuous and categorical variables, respectively. Analysis of covariance (ANCOVA) models with age, sex, and vascular risk factors as covariates were used to test group differences in amyloid SUVR and regional CBF. All aforementioned models were then run with an additional covariate for the *APOE* ε4 genotype (i.e., presence or absence

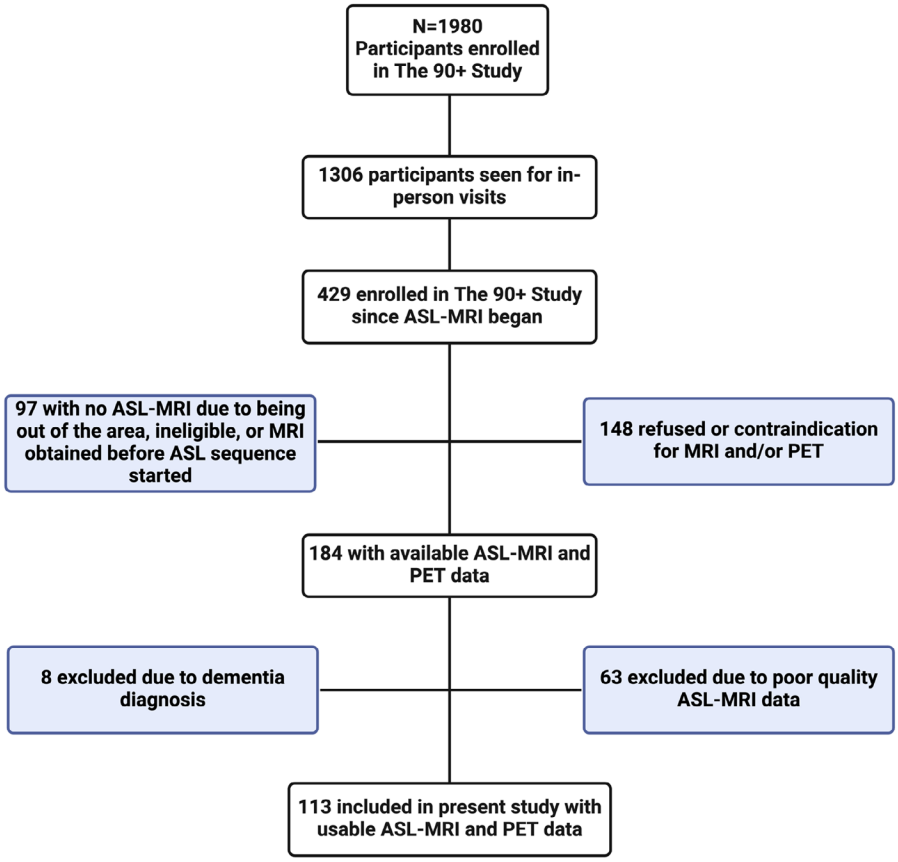

FIGURE 1 Flow chart of participant inclusion/exclusion. Flow chart displaying how study $n = 113$ was determined after participant inclusion/exclusion.

TABLE 1 Clinical, demographic, and neuroimaging characteristics for CN and CIND groups.

	CN	CIND	F or χ^2	*p*-value
N	76	37		
Age (mean [SD])	92.7 (2.3)	93.1 (2.4)	0.58	0.449
Females, *n* (%)	46 (61%)	26 (70%)	1.02	0.312
Aβ-PET positivity, *n* (%)	33 (43%)	22 (59%)	0.89	0.344
APOE ε4+, *n* (%)[a]	10 (14%)	6 (22%)	0.89	0.345
1+ vascular risk factors, *n* (%)[b]	59 (78%)	28 (76%)	0.05	0.817

Note: F-statistic indicates results of ANOVA (age), with mean (SD) displayed. χ^2-statistic indicates the results of the chi-square test (sex, Aβ-PET positivity, *APOE* ε4, vascular risk factors), with *n* (% of group) displayed.
Abbreviations: Aβ, amyloid beta; ANOVA, analysis of variance; *APOE* ε4, apolipoprotein ε4; CBF, cerebral blood flow; CIND, cognitively impaired, no dementia; CN, cognitively normal; GM, gray matter; MRI, magnetic resonance imaging; pCASL, pseudo-continuous arterial spin labeling; PCC, posterior cingulate cortex; PCu, precuneus; PET, positron emission tomography; ROI, region of interest; SD, standard deviation; SUVR, standardized uptake value ratio.
[a]Total $N = 97$; 6 CN and 10 CIND participants did not have available *APOE* ε4 data.
[b]Vascular risk factors included history of hypertension, stroke, heart disease, transient ischemic attack, and diabetes.

of one or more ε4 alleles) in the subset with genetic data available. Univariate and multiple linear regression models (controlling for age, sex, vascular risk factors, and *APOE* ε4 status) examined relationships between PCC+PCu amyloid SUVR and PCC+PCu regional CBF. All statistical analyses were performed in R project 4.2.1, RStudio, IBM SPSS Statistics version 27, and Graphpad Prism.

3 | RESULTS

Descriptive statistics for the entire sample ($N = 113$) are presented in Table 1. Participants who were CN ($n = 76$) were on average 92.7 years of age (range: 90–101), 61% female, 43% Aβ-PET positive, 14% *APOE* ε4 carriers (10/70 with available data), and 78% had one or more vascular

TABLE 2 Group differences by cognitive diagnosis in amyloid beta and cerebral perfusion (raw values and controlling for age, sex, and vascular risk factors).

	CN	CIND	F	*p*-value
N	76	37		
Aβ-PET				
PCC+PCu SUVR (raw)	0.752 (0.066)	0.775 (0.073)	2.936	0.089
PCC+PCu SUVR (adjusted)	0.752 (0.008)	0.774 (0.011)	2.592	0.110
pCASL-MRI				
Whole brain GM CBF (raw)	40.382 (7.186)	38.428 (8.724)	1.595	0.209
Whole brain GM CBF (adjusted)	40.373 (0.899)	38.446 (1.291)	1.489	0.225
Normalized ROI[a]				
PCC+PCu (raw)	1.063 (0.075)	1.024 (0.114)	4.657	0.033
PCC+PCu (adjusted)	1.064 (0.010)	1.022 (0.015)	5.463	0.021
PCC (raw)	1.106 (0.129)	1.067 (0.188)	1.695	0.196
PCC (adjusted)	1.108 (0.017)	1.063 (0.025)	2.250	0.136
PCu (raw)	1.019 (0.088)	0.981 (0.099)	4.351	0.039
PCu (adjusted)	1.019 (0.010)	0.981 (0.015)	4.387	0.039
Medial temporal (raw)	0.912 (0.097)	0.946 (0.104)	3.023	0.085
Medial temporal (adjusted)	0.912 (0.012)	0.946 (0.017)	2.875	0.093
Orbitofrontal (raw)	0.838 (0.126)	0.931 (0.148)	12.109	0.0007
Orbitofrontal (adjusted)	0.837 (0.015)	0.934 (0.022)	13.082	0.0005
Inferior parietal (raw)	0.923 (0.082)	0.889 (0.084)	4.284	0.041
Inferior parietal (adjusted)	0.923 (0.009)	0.888 (0.014)	4.392	0.038

Note: F-statistic indicates results of ANOVA with a raw mean (SD) displayed, or ANCOVA controlling for age, sex, and presence/absence of one or more vascular risk factors with an estimated marginal mean (SE) displayed.
Abbreviations: Aβ, amyloid-beta; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CBF, cerebral blood flow; CIND, cognitively impaired, no dementia; CN, cognitively normal; GM, gray matter; MRI, magnetic resonance imaging; pCASL, pseudo-continuous arterial spin labeling; PCC, posterior cingulate cortex; PCu, precuneus; RO, region of interest; SD, standard deviation; SE, standard error; SUVR, standardized uptake value ratio.
[a]ROIs were normalized to whole brain GM CBF via division.

risk factors. Participants diagnosed with CIND ($n = 37$) were on average 93.1 years of age (range: 90–101), 70% female, 59% Aβ-PET positive, 22% *APOE* ε4 carriers (6/27 with available data), and 76% had one or more vascular risk factors. CN and CIND participants did not differ in any of these demographic or vascular risk factor variables.

Participants diagnosed with CIND had lower perfusion in the PCC+PCu ROI than CN [$F(1,111) = 4.66$, $p = 0.033$; Table 2], but groups did not differ significantly in amyloid burden in the same PCC+PCu ROI [$F(1,111) = 2.94$, $p = 0.089$; Table 2]. When controlling for age, sex, and vascular risk factors, participants diagnosed with CIND had a similarly lower PCC+PCu perfusion to that of CN [$F(1,108) = 5.46$, $p = 0.021$; Figure 2A; Table 2; Figure S1] but groups did not differ significantly in amyloid burden [$F(1,108) = 2.59$, $p = 0.110$; Figure 2B; Table 2; Figure S1]. Findings were unchanged when including a continuous versus binary covariate for number of vascular risk factors or when controlling for physical activity (Tables S1–S3). When performing analyses in the subset of 97 participants with *APOE* information, similar group differences in PCC+PCu perfusion (CIND < CN) [$F(1,91) = 8.47$, $p = 0.005$] but not amyloid [$F(1,91) = 2.53$, $p = 0.115$] were observed after additional adjustment for *APOE* ε4+ status. PCC+PCu amyloid was not related to PCC+PCu perfusion in univariate and multiple linear regression models controlling for covariates (Table S4).

In covariate-adjusted models for other brain regions, perfusion was lower in CIND compared to CN in posterior brain regions, including the PCu [$F(1,108 = 4.39$, $p = 0.039$] and inferior parietal lobe [$F(1,108 = 3.49$, $p = 0.038$] (Figure 2D,E; Table 2). Orbitofrontal perfusion was higher in CIND compared to CN [$F(1,108 = 13.08$, $p = 0.0005$] (Figure 2G; Table 2). Groups did not differ significantly but showed trends for differences in PCC [$F(1,108 = 2.25$, $p = 0.136$], medial temporal [$F(1,108 = 2.88$, $p = 0.093$], and global GM perfusion [$F(1,108 = 1.49$, $p = 0.225$] (Figure 2C,F,H; Table 2).

4 | DISCUSSION

In the present study we characterized cerebral perfusion and amyloid patterns in a cohort of 113 participants 90 years of age and older. We found that those participants with cognitive impairment had lower regional perfusion in a combined AD risk region (PCC+PCu) than unimpaired individuals, but that groups did not differ significantly

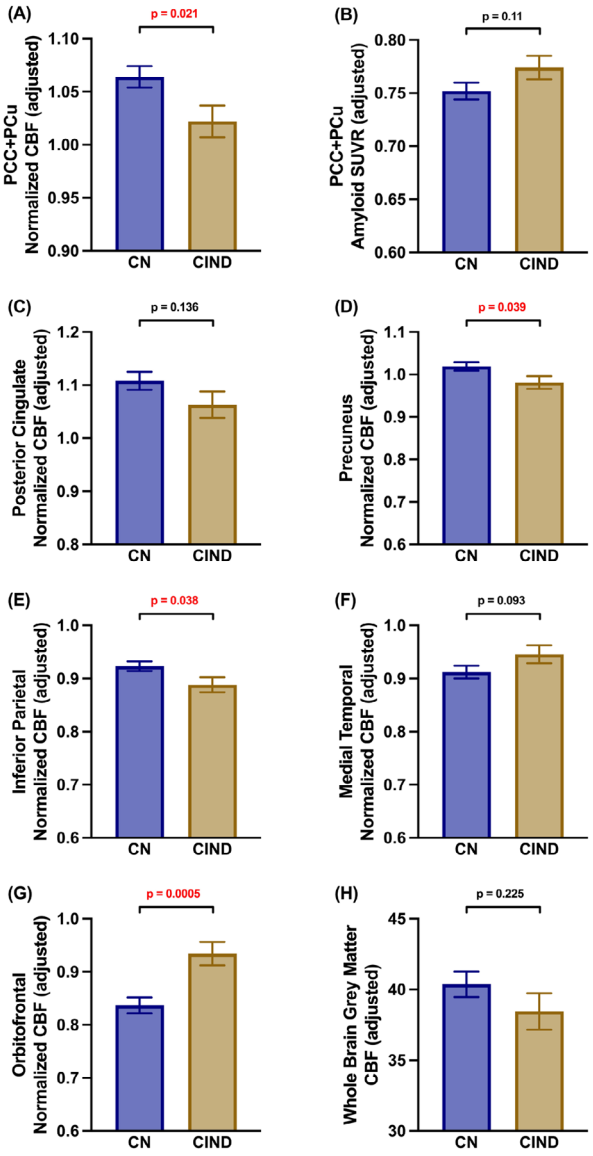

FIGURE 2 Aβ and cerebral perfusion across regions of interest by cognitive diagnosis. (A) Cerebral perfusion and (B) Aβ SUVR in a combined PCC+PCu region compared between CN and CIND groups. Across other regions, cerebral perfusion in (C) posterior cingulate, (D) precuneus, (E) inferior parietal lobe, (F) medial temporal lobe, (G) orbitofrontal cortex, and (H) global GM perfusion compared between CN and CIND groups. Regional cerebral perfusion is normalized to whole brain perfusion. Bar graphs show adjusted mean values, standard errors, and *p*-values corresponding to the results of ANCOVA models testing difference of means while controlling for age, sex, and vascular risk factors. Aβ, amyloid beta; CIND, cognitively impaired, no dementia; CN, cognitively normal; GM, gray matter; PCC, posterior cingulate cortex; PCu, precuneus; SUVR, standard uptake value ratio.

in amyloid burden in the same region. Additional regional perfusion analyses indicated lower posterior cingulate and inferior parietal perfusion in participants diagnosed with CIND relative to CN. Anteriorly, orbitofrontal perfusion was higher in participants diagnosed with CIND relative to CN. Observed effects were robust to sensitivity analyses controlling for age, sex, and vascular risk factors, as well as in a subset of participants with available *APOE* ε4 data. This represents, to our knowledge, the first study to characterize regional perfusion patterns among individuals 90 years of age and older and demonstrates CBF differences in the absence of statistically significant amyloid differences.

Studies in the young-old have frequently reported overall lower CBF in cognitively impaired individuals relative to controls,[32,39,40] with specific reduction in the posterior cingulate, parietal lobes, and temporal lobes in cognitively impaired individuals who later went on to develop AD dementia.[30–32,41] One previous study noted the specific utility of CBF in a combined PCC+PCu region in differentiating healthy controls from those with mild cognitive impairment,[42] which we similarly found in our oldest-old cohort. Although CIND participants had overall lower perfusion in the PCC+PCu, some showed perfusion levels comparable to CN. The present study found no correlation between amyloid burden and CBF. Further studies should explore whether heterogeneity in hypoperfusion may be related to other pathophysiological factors. We also observed hyperperfusion specifically within the orbitofrontal cortex in CIND relative to CN. This is consistent with prior studies reporting frontal hyperperfusion in MCI relative to CN.[43,44,41] Frontal hyperperfusion may represent an early pathologic or compensatory change, but the literature is mixed[46] and more studies are needed. Our findings add to the growing cerebral perfusion literature by characterizing, for the first time, patterns of altered perfusion in the precuneus, posterior cingulate, parietal, and frontal regions in oldest-old participants with and without cognitive impairment. The *APOE* ε4 allele confers specific risk for altered perfusion patterns among cognitively intact and impaired young-old individuals,[46–49] but our findings remained consistent even when controlling for *APOE* ε4 carrier status, suggesting that the group perfusion differences we observed are robust.

We observed no difference in amyloid burden between CN and CIND, consistent with prior studies.[38] Some studies in the oldest-old find that amyloid burden predicts future dementia,[11,35,50,51] but others suggest that amyloidosis does not always lead to dementia in this population.[52,11] Studies examining CBF in the oldest-old are lacking, with the few existing studies in slightly younger (i.e., mean age of 85) participants finding that regional CBF predicted the development of white matter hyperintensities and a broader loss of white matter integrity.[11–13] Our characterization of regional perfusion points to the importance of characterizing cerebrovascular health in the oldest-old, especially in those earlier in disease processes with only mild levels of impairment. Cerebral perfusion may ultimately be more robust in detecting early changes in cognition, whereas amyloidosis may relate more to dementia onset, which we aim to characterize in future studies.

Limitations to the present study include the cross-sectional study design, potential selection bias (i.e., only inclusion of those with available perfusion and amyloid-PET data), homogenous sample (i.e., highly educated and majority White identifying), lack of characterization of tau, and sample size limiting detection of small effects. Our study offers significant novelty in that it represents the first effort to characterize regional perfusion profiles in this population and compare perfusion

to amyloid. Perfusion, but not amyloid, differences were statistically significant when controlling for numerous other factors, including age, sex, presence of vascular risk factors, and *APOE* ε4 in a subset of participants.

Overall, in a cohort of dementia-free participants in the oldest-old segment of the population, cerebral perfusion, but not amyloid, differed significantly between groups with and without cognitive impairment, and we found perfusion differences in regions vulnerable to age-related processes (e.g., posterior cingulate, precuneus, inferior parietal lobe, and orbitofrontal cortex). Future efforts may aim to compare perfusion and amyloid to levels of tau aggregation (e.g., via tau-PET), as characterizing cerebrovascular/amyloid/tau profiles in the oldest-old may offer unique insights into factors that buffer against the deleterious effects of aging leading to cognitive decline.

ACKNOWLEDGMENTS

The authors thank the participants and their relatives, testers, examiners, and staff of *The 90+ Study*. This research was supported by National Institutes of Health (NIH) grants (D.A.N.: R01AG064228, R01AG060049, R01AG082073, P01AG052350, and P30AG066530; S.A.S.: R01AG062706; C.H.K. and M.M.C.: R01AG021055; and C.D.: U19NS120384, P30AG072972, RF1AG054548, R56AG048642, and R01AG075758). Apolipoprotein E (*APOE*) genotyping done by the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD)/National Institute on Aging (NIA), which receives government support under a cooperative agreement grant (U24AG021886) awarded by the National Institute on Aging (NIA), was used in this study.

CONFLICT OF INTEREST STATEMENT

The authors have no disclosures and no competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided written informed consent.

ORCID

Daniel A. Nation https://orcid.org/0000-0002-9123-0658

REFERENCES

1. Wolters FJ, Zonneveld HI, Hofman A, et al. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation*. 2017;136:719-728. doi:10.1161/CIRCULATIONAHA.117.027448
2. Zonneveld HI, Loehrer EA, Hofman A, et al. The bidirectional association between reduced cerebral blood flow and brain atrophy in the general population. *J Cereb Blood Flow Metab*. 2015;35:1882-1887. doi:10.1038/jcbfm.2015.157
3. Wierenga CE, Hays CC, Zlatar ZZ. Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *J Alzheimers Dis*. 2014;42:S411-S419. doi:10.3233/JAD-141467
4. Korte N, Nortley R, Attwell D. Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. *Acta Neuropathol*. 2020;140:793-810. doi:10.1007/s00401-020-02215-w
5. Coomans EM, van Westen D, Binette AP, et al. Interactions between vascular burden and amyloid-β pathology on trajectories of tau accumulation. *Brain*. 2024;147:949-960. doi:10.1093/brain/awad317
6. de la Torre J. The vascular hypothesis of Alzheimer's disease: a key to preclinical prediction of dementia using neuroimaging. *J Alzheimers Dis*. 2018;63:35-52. doi:10.3233/JAD-180004
7. Solis E, Hascup KN, Hascup ER. Alzheimer's disease: the link between amyloid-β and neurovascular dysfunction. *J Alzheimers Dis*. 2020;76:1179-1198. doi:10.3233/jad-200473
8. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC; Alzheimer's Disease Neuroimaging Initiative. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun*. 2016;7:11934. doi:10.1038/ncomms11934
9. Bullain SS, Corrada MM. Dementia in the oldest old. *Continuum*. 2013;19:457-469. doi:10.1212/01.CON.0000429172.27815.3f
10. Kawas C, Corrada M. Alzheimers and dementia in the oldest-old: a century of challenges. *Curr Alzheimer Res*. 2006;3:411-419. doi:10.2174/156720506779025233
11. Woodworth DC, Scambray KA, Corrada MM, Kawas CH, Sajjadi SA. Neuroimaging in the oldest-old: a review of the literature. *J Alzheimers Dis*. 2021;82:129-147. doi:10.3233/jad-201578
12. Promjunyakul NO, Lahna DL, Kaye JA, et al. Comparison of cerebral blood flow and structural penumbras in relation to white matter hyperintensities: a multi-modal magnetic resonance imaging study. *J Cereb Blood Flow Metab*. 2016;36:1528-1536. doi:10.1177/0271678X16651268
13. Promjunyakul N, Lahna D, Kaye JA, et al. Characterizing the white matter hyperintensity penumbra with cerebral blood flow measures. *Neuroimage Clin*. 2015;8:224-229. doi:10.1016/j.nicl.2015.04.012
14. Corrada MM, Hayden KM, Paganini-Hill A, et al. Age of onset of hypertension and risk of dementia in the oldest-old: the 90+ Study. *Alzheimers Dement*. 2017;13:103-110. doi:10.1016/j.jalz.2016.09.007
15. van Rijssel AE, Stins BC, Beishon LC, et al. Effect of antihypertensive treatment on cerebral blood flow in older adults: a systematic review and meta-analysis. *Hypertension*. 2022;79:1067-1078. doi:10.1161/HYPERTENSIONAHA.121.18255
16. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: the 90+ study. *Curr Alzheimer Res*. 2013;9:709-717. doi:10.2174/156720512801322537
17. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet North Am Ed*. 1997;349:1793-1796. doi:10.1016/S0140-6736(97)01007-6
18. Melikyan ZA, Corrada MM, Dick MB, Whittle C, Paganini-Hill A, Kawas CH. Neuropsychological test norms in cognitively intact oldest-old. *J Int Neuropsychol Soc*. 2019;25:530-545. doi:10.1017/S1355617719000122
19. Dai W, Garcia D, De Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med*. 2008;60:1488-1497. doi:10.1002/mrm.21790
20. Dai W, Fong T, Jones RN, et al. Effects of arterial transit delay on cerebral blood flow quantification using arterial spin labeling in an elderly cohort. *J Magn Reson Imaging*. 2017;45:472-481. doi:10.1002/jmri.25367
21. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative 3: continued innovation for clinical trial improvement. *Alzheimers Dement*. 2017;13:561-571. doi:10.1016/j.jalz.2016.10.006
22. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled Perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med*. 2015;73:102-116. doi:10.1002/mrm.25197
23. Yew B, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Cerebrovascular resistance: effects on cognitive decline, cortical atrophy,

and progression to dementia. *Brain*. 2017;140:1987-2001. doi:10.1093/brain/awx112
24. Nation DA, Wierenga CE, Clark LR, et al. Cortical and subcortical cerebrovascular resistance index in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis*. 2013;36:689-698. doi:10.3233/JAD-130086
25. Clark AL, Weigand AJ, Bangen KJ, Merritt VC, Bondi MW, Delano-Wood L. Repetitive mTBI is associated with age-related reductions in cerebral blood flow but not cortical thickness. *J Cereb Blood Flow Metab*. 2021;41:431-444. doi:10.1177/0271678X19897443
26. Bangen KJ, Nation DA, Clark LR, et al. Interactive effects of vascular risk burden and advanced age on cerebral blood flow. *Front Aging Neurosci*. 2014;6:159. doi:10.3389/fnagi.2014.00159
27. Petr J, Mutsaerts HJMM, De Vita E, et al. Effects of systematic partial volume errors on the estimation of gray matter cerebral blood flow with arterial spin labeling MRI. *MAGMA*. 2018;31:725-734. doi:10.1007/s10334-018-0691-y
28. Rolls ET, Huang CC, Lin CP, Feng J, Joliot M. Automated anatomical labelling atlas 3. *Neuroimage*. 2020;206:116189. doi:10.1016/j.neuroimage.2019.116189
29. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003;19:1233-1239. doi:10.1016/S1053-8119(03)00169-1
30. Chao LL, Pa J, Duarte A, et al. Patterns of cerebral hypoperfusion in amnestic and dysexecutive MCI. *Alzheimer Dis Assoc Disord*. 2009;23:245-252. doi:10.1097/WAD.0b013e318199ff46
31. Chen Y, Wolk DA, Reddin JS, et al. Voxel-level comparison of arterial spin-labeled perfusion MRI and FDG-PET in Alzheimer disease. *Neurology*. 2011;77:1977-1985. doi:10.1212/WNL.0b013e31823a0ef7
32. Desai B, Edwards O, Beishon L. The role of cerebral blood flow in the pathogenesis of Alzheimer's Disease Dementia. *Aging Health Res*. 2024;4:100188. doi:10.1016/j.ahr.2024.100188
33. Duan W, Zhou GD, Balachandrasekaran A, et al. Cerebral blood flow predicts conversion of mild cognitive impairment into Alzheimer's disease and cognitive decline: an arterial spin labeling follow-up study. *J Alzheimers Dis*. 2021;82:293-305. doi:10.3233/jad-210199
34. Aslan S, Lu H. On the sensitivity of ASL MRI in detecting regional differences in cerebral blood flow. *Magn Reson Imaging*. 2010;28:928-935. doi:10.1016/j.mri.2010.03.037
35. Kawas CH, Greenia DE, Bullain SS, et al. Amyloid imaging and cognitive decline in nondemented oldest-old: the 90+ Study. *Alzheimers Dement*. 2013;9:199-203. doi:10.1016/j.jalz.2012.06.005
36. Sajjadi SA, Fletcher E, Sheikh-Bahaei N, et al. The relation between amyloid imaging and amyloid pathology in the oldest old: the 90+ Study. *Alzheimers Dement*. 2019;15:P1124-P1125. doi:10.1016/j.jalz.2019.06.3464
37. Wang J, Ackley S, Woodworth DC, et al. Associations of amyloid burden, white matter hyperintensities, and hippocampal volume with cognitive trajectories in the 90+ study. *Neurology*. 2024;103:e209665. doi:10.1212/WNL.0000000000209665
38. Lau WL, Fisher M, Fletcher E, et al. Kidney function is not related to brain amyloid burden on PET imaging in the 90+ study cohort. *Front Med*. 2021;8:671945. doi:10.3389/fmed.2021.671945
39. Johnson KA, Albert MS. Perfusion abnormalities in prodromal AD. *Neurobiol Aging*. 2000;21:289-292. doi:10.1016/S0197-4580(00)00137-8
40. Zhang H, Wang Y, Lyu D, et al. Cerebral blood flow in mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *Ageing Res Rev*. 2021;71:101450. doi:10.1016/j.arr.2021.101450
41. Duan W, Sehrawat P, Balachandrasekaran A, et al. Cerebral blood flow is associated with diagnostic class and cognitive decline in Alzheimer's disease. *J Alzheimers Dis*. 2020;76:1103-1120. doi:10.3233/jad-200034
42. Thomas B, Sheelakumari R, Kannath S, Sarma S, Menon RN. Regional cerebral blood flow in the posterior cingulate and precuneus and the entorhinal cortical atrophy score differentiate mild cognitive impairment and dementia due to Alzheimer disease. *AJNR Am J Neuroradiol*. 2019;40:1658-1664. doi:10.3174/ajnr.A6219
43. Camargo A, Wang Z. Hypo- and hyper-perfusion in MCI and AD identified by different ASL MRI sequences. *Brain Imaging Behav*. 2023;17:306-319. doi:10.1007/s11682-023-00764-8
44. Ding B, Ling HW, Zhang Y, et al. Pattern of cerebral hyperperfusion in Alzheimer's disease and amnestic mild cognitive impairment using voxel-based analysis of 3D arterial spin-labeling imaging: initial experience. *Clin Interv Aging*. 2014;9:493-500. doi:10.2147/CIA.S58879
45. Huang Q, Cao X, Chai X, Wang X, Xu L, Xiao C. Three-dimensional pseudocontinuous arterial spin labeling and susceptibility-weighted imaging associated with clinical progression in amnestic mild cognitive impairment and Alzheimer's disease. *Medicine*. 2019;98:e15972. doi:10.1097/MD.0000000000015972
46. Hays CC, Zlatar ZZ, Meloy MJ, et al. Interaction of APOE, cerebral blood flow, and cortical thickness in the entorhinal cortex predicts memory decline. *Brain Imaging Behav*. 2020;14:369-382. doi:10.1007/s11682-019-00245-x
47. Hays CC, Zlatar ZZ, Meloy MJ, et al. APOE modifies the interaction of entorhinal cerebral blood flow and cortical thickness on memory function in cognitively normal older adults. *Neuroimage*. 2019;202:116162. doi:10.1016/j.neuroimage.2019.116162
48. Wierenga CE, Dev SI, Shin DD, et al. Effect of mild cognitive impairment and APOE genotype on resting cerebral blood flow and its association with cognition. *J Cereb Blood Flow Metab*. 2012;32:1589-1599. doi:10.1038/jcbfm.2012.58
49. Tai LM, Thomas R, Marottoli FM, et al. The role of APOE in cerebrovascular dysfunction. *Acta Neuropathol*. 2016;131:709-723. doi:10.1007/s00401-016-1547-z
50. Lopez OL, Klunk WE, Mathis C, et al. Amyloid, neurodegeneration, and small vessel disease as predictors of dementia in the oldest-old. *Neurology*. 2014;83:1804-1811.
51. Lopez OL, Becker JT, Chang Y, et al. Amyloid deposition and brain structure as long-term predictors of MCI, dementia, and mortality. *Neurology*. 2018;90:e1920-e1928. doi:10.1212/WNL.0000000000005549
52. Mathis CA, Kuller LH, Klunk WE, et al. In vivo assessment of amyloid-β deposition in nondemented very elderly subjects. *Ann Neurol*. 2013;73:751-761. doi:10.1002/ana.23797

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dutt S, Woodworth DC, Sajjadi SA, et al. Cerebral perfusion and amyloidosis in the oldest-old. *Alzheimer's Dement*. 2024;20:9068–9075. https://doi.org/10.1002/alz.14357