Daniel A. Nation, Ph.D.

Assistant Professor of Psychology
University of Southern California

The Role of Vascular Aging in Cognitive Decline & Alzheimer’s Disease
Vascular Aging & Alzheimer’s Disease
Age-Related Arterial Stiffening

The Compliant Vessel vs the Noncompliant Vessel

Compliant
Systole Diastole

Constant Stroke Volume

Aorta

Noncompliant
Systole Diastole

Pulse Pressure

• Pulse pressure = Systolic – Diastolic Pressure
Vascular Aging & Cognition

- Qiu et al., 2003, *Stroke*
- Waldstein et al., 2008, *Hypertension*
- Nation et al., 2010, *JINS*
- Mitchel et al., 2011, *Brain*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Carotid–femoral PWV</th>
<th>Central pulse pressure</th>
<th>Carotid pulsatility index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta \pm SE )</td>
<td>( \beta \pm SE )</td>
<td>( \beta \pm SE )</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>Brain structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total brain parenchyma</td>
<td>(-0.044 \pm 0.042)</td>
<td>(-0.006 \pm 0.044)</td>
<td>(-0.127 \pm 0.037)</td>
</tr>
<tr>
<td>Grey matter</td>
<td>(-0.064 \pm 0.042)</td>
<td>(0.027 \pm 0.044)</td>
<td>(-0.079 \pm 0.038)</td>
</tr>
<tr>
<td>White matter</td>
<td>(-0.039 \pm 0.044)</td>
<td>(-0.065 \pm 0.046)</td>
<td>(-0.128 \pm 0.039)</td>
</tr>
<tr>
<td>White matter hyperintensities</td>
<td>(0.108 \pm 0.045)</td>
<td>(-0.021 \pm 0.048)</td>
<td>(0.017 \pm 0.041)</td>
</tr>
<tr>
<td>Cognitive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>(-0.095 \pm 0.043)</td>
<td>(-0.114 \pm 0.045)</td>
<td>(-0.165 \pm 0.039)</td>
</tr>
<tr>
<td>Speed</td>
<td>(0.027 \pm 0.037)</td>
<td>(-0.018 \pm 0.039)</td>
<td>(-0.118 \pm 0.033)</td>
</tr>
<tr>
<td>Executive function</td>
<td>(-0.076 \pm 0.045)</td>
<td>(-0.094 \pm 0.048)</td>
<td>(-0.155 \pm 0.041)</td>
</tr>
</tbody>
</table>
The graph shows the beta coefficient (95% confidence interval) for Pulse Pressure in APOE4 carriers. The y-axis represents the beta coefficient, and the x-axis represents the different APOE4 carrier statuses.

- **APOE4- (N=409)**: The beta coefficient is approximately 0.002 with a 95% confidence interval ranging from -0.006 to 0.010. The P-value is 0.19.
- **APOE4+ (N=122)**: The beta coefficient is approximately 0.004 with a 95% confidence interval ranging from -0.008 to 0.016. The P-value is 0.02.

The graph indicates a statistically significant difference in Pulse Pressure between APOE4 carriers and non-carriers, with the APOE4+ group showing a higher beta coefficient compared to the APOE4- group.

• 5 mmHg pulse pressure → 36% increase in odds of AD+CVD
• Accounted for ~12% of variance in CVD severity
• No relationship with Braak stage or cerebral amyloid angiopathy
**Aβ Clearance Mechanisms**

Image from Weller et al., 2009, *Acta Neuropathol*
Aβ Clearance Mechanisms

Iliff et al., 2012, Science Translational Medicine

The glymphatic pathway

Para-arterial influx

Paravenous clearance

Interstitial fluid and solute clearance

AQP4
Water flux

Para-arterial influx
Paravenous efflux
Interstitial solutes
Solute clearance
- Pulse pressure and reduced Aβ clearance
  - Langbaum et al., 2012, *Neurobiology of Aging*
  - Rodrigue et al., 2013, *JAMA Neurology*
  - Hughes et al., 2014, *Neurology - PWV*
  - Hughes et al., 2015, *JAMA Neurology – very-old*
Pulse Pressure & CSF Biomarkers

**Nation et al., Neurology, 2013**

- Cognitively normal, N = 175
- Healthy older adults
- \( A\beta_{42} \):
  - \( \beta = -0.87, p = 0.050 \)
- P-tau:
  - \( \beta = 0.28, p = 0.006 \)
- P-tau: \( A\beta \):
  - \( \beta = 0.0023, p = 0.002 \)
By using the cohort under study to define a cognitive cutpoint, we lacked an independent means of defining abnormality. This meant that a fixed proportion (5%, 10%, 15%) of subjects were designated as cognitively impaired. This has obvious potential for erroneously classifying a few subjects at the margin as abnormal who might not have been with a slightly different definition of abnormal. We suspect that this effect underlies many of our unclassified subjects. The problem of using cognitive impairment as both a criterion for preclinical AD and as an outcome in longitudinal observational studies and therapeutic trials will need further exploration. Thus, operationalization of criteria for subtle cognitive impairment is complex, and the definition of the cognitive threshold we have provisionally chosen can likely be improved upon.

As ours is a population-based study, our CN subjects differ from those recruited into studies such as the Alzheimer's Disease Neuroimaging Initiative or other clinic-based samples. Age, education, and comorbidities greatly influence the likelihood and rate of progressing to dementia, and therefore evaluating new diagnostic criteria in samples that approximately reflect these variables as they exist in the general population is essential for generalizability and external validity of results.

The high prevalence of SNAP in this preliminary exercise underscores the importance of performing studies that have as few implicit inclusion and exclusion criteria for subjects as possible. Results might be different from samples drawn from memory clinics, where recruitment biases might reduce the number of non-AD etiologies. Although the new NIA-AA preclinical criteria broke new ground conceptually, many operational issues were not addressed. These include standardization of biomarker measures, defining biomarker cutpoints, how to address discrepancies within biomarker class (eg, abnormal FDG but normal hippocampal volume), the definition of subtle cognitive impairment, and how to address the non-AD pathophysiological processes that are present in elderly populations. Some limitations of our study include the fact that our subjects had only MRI and PET imaging biomarkers available, not CSF. The number of cognitive testing sessions, and hence practice effects, varied among subjects in our cohort. Other important options remain to be evaluated, including alternative biomarker and cognitive cutpoints and alternative imaging measures. However, with this operational approach to implementation, the NIA-AA preclinical AD guidelines function adequately in a population-based sample of elderly subjects and, therefore, should be useful in planning future observational and therapeutic studies.

**Acknowledgment**

The Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation, USA, and the Robert H. and Clarice Smith Alzheimer's Disease Research Program of the Mayo Foundation, USA. This study was supported by the NIH/National Institute on Aging (R01 AG11378, U01 AG006786, P50 AG16574, C06 RR018898; C.R.J.).

**Authorship**

C.R.J. and D.S.K. contributed equally to this work.

**Potential Conflicts of Interest**


**FIGURE 4:** Venn diagram depicting the distribution of all 450 cognitively normal subjects by National Institute on Aging–Alzheimer's Association stage, biomarker, and cognitive status. AD = Alzheimer disease.
Pulse Pressure & CSF Biomarkers

Nation et al., 2015, *JAMA Neurology*

![Graph showing pulse pressure comparison between Aβ-Ptau- and Aβ+Ptau- groups for Young-Old and Very-Old participants.](image)

- **Young-Old**:
  - *p < .05 vs. Aβ+Ptau-**
  - †*p < .05 vs. Aβ+Ptau-
  - ‡*p = .07 vs. Aβ-Ptau-

- **Very-Old**:
  - ‡*p < .001 vs. Aβ-Ptau-
  - *p = .06 vs. Aβ+Ptau-
Pulse Pressure & Preclinical AD

Nation et al., in preparation
Edmonds et al., Journal of Alzheimer’s Disease
• Cerebrovascular stiffening

• Cerebrovascular Resistance = MAP – ICP / CBF

• Ratio of Arterial Pressure ($P_\alpha$) to CBF (mL/100g/min)
  – CVR = $P_\alpha$ / CBF

Buxton, 2005, *Introduction to Functional Magnetic Resonance Imaging*
Estimates of Cerebrovascular Stiffening

- Arterial spin labeling MRI - CBF
- MRI-compatible blood pressure monitoring
  - $\text{CVRi}_{\text{MAP}} = \text{MAP} / \text{CBF}$
  - $\text{CVRi}_{\text{Pulse Pressure}} = \text{Pulse pressure} / \text{CBF}$
Blood Pressure $\rightarrow$ Regional CBF

- CVRi

+ CVRi

Cerebral Blood Flow

Blood Pressure
CV Ri in MCI & AD

Nation et al., 2013, Journal of Alzheimer’s Disease

A) NC vs AD

B) MCI vs AD
NC < MCI < AD

Nation et al., 2013, Journal of Alzheimer’s Disease
CVRi changes with Aging

Clark, Nation, et al., 2015, Alzheimer’s Research & Therapy
Estimates of Cerebrovascular Stiffening

- Arterial spin labeling MRI
- MRI-compatible blood pressure monitoring
  - Vascular compliance = \( \Delta \text{CBF} / \Delta \text{BP} \)
  - \( \text{VC} = \text{CBF}_{\text{systolic}} - \text{CBF}_{\text{diastolic}} / \text{Pulse pressure} \)
- Yan et al., 2015, Neuroimage
Future Directions

A. Cerebrovascular stiffness

B. Peripheral arterial stiffening

NVU injury & BBB damage
- Vascular adhesion
- Angiogenic response
- Pericyte loss
- Toxin extravasation
- Toxin clearance

Cerebrovascular Lesions
Amyloidosis
Neurodegeneration

Manifest Cognitive Decline
- Subtle Cognitive Decline
- Mild Cognitive Impairment
- Functional Decline
Dementia

Blood Flow Regulation
- Microvascular Permeability
- Cell Matrix Interactions
- Neurotransmitter Turnover
Endothelium
Pericytes
Neurons
Glia

Angiogenesis
Neurogenesis
Acknowledgements

- Berislav Zlokovic, M.D., Ph.D.
- Helena Chui, M.D.
- Mark Bondi, Ph.D.
- Thomas Liu, Ph.D.
- Katherine Bangen, Ph.D.
- Lisa Delano-Wood, Ph.D.
- Douglas Galasko, Ph.D.
- David Salmon
- Lindsay Clark, Ph.D.
- Belinda Yew, M.A.
- Participants in ADNI study