Vascular Risk Factors Cause AD?
What do we mean in the age of AD-Biomarkers and Bioinformatics?

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Introduction

1. Epidemiological studies indicate that Vascular Risk Factors increase the risk for incident Alzheimer disease, but apart from ApoE4 [which increases amyloid deposition in both the blood vessels and brain parenchyma], the explanation(s) or mechanism(s) are unknown.
   a. VRF increase the risk of vascular brain injury (i.e., infarcts and hemorrhages), and therefore dementia due to mixed etiologies (AD+CVD).
   b. Animal and human studies suggest possible interactions between vascular factors and accumulation of beta-amyloid in the brain. (Mechanisms are still unproven in humans)

2. Vascular risk factors are modifiable.
   a. Undoubtedly, decreasing VRF will decrease the risk of “AD”.
   b. Will decreasing VRF also decrease AD?
Projected: 10% vascular risk reduction x 10 Yrs
8% reduction in new cases of “AD”

Projected Number of cases prevented

- 10% reduction
- 25% reduction

Number of AD cases prevented in the USA

- Diabetes mellitus
- Midlife hypertension
- Midlife obesity
- Physical inactivity
- Smoking
- Depression
- Cognitive inactivity
- Combined

What do we mean by “AD”? *AD* = Biomarker Standard

**Do Not Mean**

- “AD” defined as progressive dementia without clinical evidence of stroke (defined solely based on history, exam, neuropsychology, or structural MRI/CT).
- Mixed AD+VCI

**Do Mean**

- *AD* defined by widespread beta-amyloid plaques and p-Tau neurofibrillary tangles.
  - Beta-amyloid by CSF, PET, or neuropathology
  - P-Tau by CSF, PET or neuropathology

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H&P  | Neuropsych  | CT/MRI  | FDG  | Abeta/Tau Biomarker
---  | ---         | ---     | ---  | ---
2004: Imaging β-Amyloid during life with Pittsburgh Compound B (PIB)

Associations Between VRFs and AD: Parallel or Interactive pathways? Mediation vs Moderation?

VRF (HTN, DM, Lipids) → CVD (Athero, Arteriolo) → Blood Brain Barrier → VBI → Brain Structure/Fn (Cortical thickness, Hip Volume, WMHs, Synapses) → Cognition

ApoE4 → Beta-amyloid → Tauopathy

AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts

Clinical Dx → Activities of Daily Living

AD VCI Mixed
NIH Non-AD Summit May 1-2, 2013
Bethesda, Maryland
(T Montine et al)

Topic 5 - Vascular Contributions to ADRD: Focus on
........AD/Vascular Interactions

Focus Area 2: Human-Based Studies

Recommendation 2 (S Craft / H Chui):

5.2.2. Determine interrelationships among
cerebrovascular disease (CVD), vascular risk
factors (VRF) with Aβ & neurodegeneration.
Associations Between VRF and AD

#1 Traditional approach
VRF and AD; CVD and AD

#3 System-based approach

VRF
HTN, DM, Lipids

ApoE4

CVD
Arterio sclerosis
Amyloid angiopathy

VBI

Brain Structure/Fn
Cortical thickness
Hip Volume
WMHs
Synapses

Clinical Dx
Cognition
Activities of Daily Living

AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts
Associations Between HTN and AD: Parallel or Interactive pathways?

AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts
Systolic BP and Pulse Pressure are associated with greater accumulation of PiB (n=10).

Langbaum J. Neurobiology of Aging 2012; 33: 827.
Three ways to clear Aβ from the brain

**Enzymatic degradation by**
Neprilysin
Insulin-degrading enzyme

**Blood clearance via LRP-1**
(low density lipoprotein receptor-related protein) is less efficient with apolipoprotein E4

**Perivascular lymphatic drainage**
(less efficient with cerebral amyloid angiopathy or arteriosclerosis)


Jonathan Kipnis,
University of Virginia.
Associations Between DM and AD: Parallel or Interactive pathways?

AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts
DM is associated with increased incident “AD”

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yr)</th>
<th>F/U (yr)</th>
<th>Numbers</th>
<th>All dementia</th>
<th>Vascular dementia</th>
<th>AD+VaD</th>
<th>Alzheimer disease</th>
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<tbody>
<tr>
<td>Yoshitake 1995</td>
<td>&gt;65</td>
<td>7</td>
<td>70 756</td>
<td>2.8</td>
<td>2.2 (0.97, 4.9)</td>
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<td>Hisayama 1985-1992</td>
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<td>2.2 (0.97, 4.9)</td>
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<tr>
<td>Ott 1999</td>
<td>&gt;55</td>
<td>2.1</td>
<td>692 5678</td>
<td>1.9</td>
<td>2.0 (0.7, 5.6)</td>
<td>3.0</td>
<td>1.8 (1.1, 3.0)</td>
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<td>Rotterdam 1990-1994</td>
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<tr>
<td>Luchsinger 2001</td>
<td>≥65</td>
<td>4.3</td>
<td>255 1007</td>
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<td>1.3 (0.8, 1.9)</td>
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<td>WHICAP 1992-1997</td>
<td>≥65</td>
<td>4-6</td>
<td>503 5071</td>
<td>1.26</td>
<td>2.03 (1.15, 3.5)</td>
<td>1.3</td>
<td>1.3 (0.83, 2.1)</td>
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<td>Peila 2002</td>
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<td>900 1674</td>
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<td>WHICAP 1999-2001</td>
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<td>2.3 (1.1, 5.0)</td>
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<td>Religious Orders Study</td>
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<td>Avantiolo 2010</td>
<td>&gt;85</td>
<td>87</td>
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<td>Vantaa 85+</td>
<td>&gt;85</td>
<td>87</td>
<td>268 697</td>
<td>1.5</td>
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<td>1.8</td>
<td>1.6 (0.9, 3.0)</td>
</tr>
</tbody>
</table>
Diabetes is associated with infarction but not AD Pathology
Religious Orders Study (n=200)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes (n=36)</th>
<th>Non diabetes (n=197)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death</td>
<td>84.4 (6.6)</td>
<td>85.8 (6.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>63.9</td>
<td>42.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Education, y</td>
<td>17.4 (4.1)</td>
<td>18.2 (3.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Dementia, %</td>
<td>50.0</td>
<td>44.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Cerebral Infarction</td>
<td>52.8</td>
<td>32.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Cortical infarction</td>
<td>19.4</td>
<td>8.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Subcortical infarction</td>
<td>50</td>
<td>26.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall AD pathology</td>
<td>0.67 (0.62)</td>
<td>0.71 (0.65)</td>
<td>0.74</td>
</tr>
<tr>
<td>Neuritic plaques</td>
<td>0.84 (0.82)</td>
<td>0.76 (0.82)</td>
<td>0.51</td>
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<tr>
<td>Diffuse plaques</td>
<td>0.77 (0.91)</td>
<td>0.83 (0.86)</td>
<td>0.60</td>
</tr>
<tr>
<td>Neurofibrillary tangles</td>
<td>0.39 (0.50)</td>
<td>0.55 (0.74)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Regional pattern of glucose hypometabolism differs in T2DM and AD

DM is associated with decreased FDG but not increased PiB amyloid (Mayo Aging Study; n=749)

Associations Between Lipids and AD: Parallel or Interactive pathways?

Dyslipidemia

Apolipoprotein E (ApoE4)

Low HDL-C

Beta-amyloid

Tauopathy

Cortical thickness

Hip Volume

WMHs

Synapses

AD biomarkers (CSF and PET amyloid/tau)

Neuropathology: Plaques, Tangles, Infarcts

Clinical Dx

Cognition

Activities of Daily Living

AD VCI Mixed

Brain Structure/Fn

Beta-amyloid Arteriolo

CAA

VBI

Blood Brain Barrier
Washington Heights Inwood Columbia Aging Project (WHICAP)

- Baseline (1992-1994) N=2,126 > 65 y/o (AA 33%; Hispanic 44%; White 22%)

- Follow-up Q 18 mo: By 2003, of 1,138 subjects, 176 developed prob AD (246 prob+poss AD) out of 1,138 subjects

- Vascular risk factors: DM, HTN, DL, Smoking

- Hazard ratios for prob AD:
  - 1 risk factor: 1.8 (1.1, 3.0)
  - 2 risk factors: 2.8 (1.7, 4.7)
  - 3 risk factors: 3.4 (1.8, 6.3)

Higher HDL-C >55 mg/dl in mid-life was associated with decreased risk of incident AD (OR=0.4 (0.2, 0.9) in WHICAP study (Reitz et al., 2010).

LDL-Cholesterol is associated with increased; while HDL cholesterol is associated with decreased brain amyloid.

Correlation between LDL-C (left) and LDL-C (right) and PIB index, controlling for HDL-D (left) or LDL-C (right panel), age, sex apoE4 status.

Statistical cortical maps showing the impact of Aβ, HDL-C and their interaction on cortical thickness in PIB+ subjects (n=22)

Aβ = -.14 (p = .07); HDL = +.45 (p < .01); Interaction = +.36 (p = .01)

Villeneuve S, et al., Neurology 2014; 83: 40-7
Increased accumulation of hippocampal β-amyloid in both male and female 3xTg Mice fed a high fat diet

Barron AM.... Pike D. PLoS One 2013;8:e78554.
Associations Between VRFs and AD: Parallel or Interactive pathways?

VRF & AD
HTN- ?
DM – No?
DL – Yes?

?LDL-C & Fatty acids

ApoE4

Blood Brain Barrier

Athero Arteriolo
CAA

VBI

Brain Structure/Fn
Cortical thickness
Hip Volume
WMHs
Synapses

AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts

Clinical Dx

Cognition
Activities of Daily Living

AD VCI Mixed
II. Effects of VRFs and AD on the Microvasculature and the Blood Brain Barrier

- VRF
- ApoE4
- Athero
- Arteriolo
- CAA
- Beta-amyloid
- Tauopathy
- VBI
- Blood Brain Barrier
- Vascular reactivity
- BBB transport
- BBB permeability
- AD biomarkers (e.g., Amyloid and Tau PET Imaging)

Clinical Dx
- AD
- VCI
- Mixed

Cognition ADLs
- Cortical thickness
- Hip Volume
- WMHs
- Synapses
Hypertension-Associated Impairment in Vasoreactivity to Hyper- and Hypo-Capnea (pCO₂)
Arterial Spin Labeling (ASL) MR Perfusion Imaging

Hajjar, I et al. Hypertension. 2011
Leaky Blood Brain Barrier in early AD hippocampus
Dynamic Contrast Enhanced (DCE)-MRI

Do vascular risk factors moderate AD?

a. **Association with Age:**
   a. HTN, DM, and DL increase with age, as does AD.

b. **Selective vulnerability:**
   a. Do VRF increase pathology in areas that are selectively vulnerable to AD? Lipid and precuneus - Yes; Diabetes and orbital frontal lobe – No

c. **Pathogenic interactions:**
   a. Do VRF increase beta-amyloid or p-Tau? Increased Pulse pressure - yes. Diabetes – no; DL - yes. If yes, how?

d. **Sequence of events:**
   a. Do VRF mediate (precede) or moderate (follow) the accumulation of AD biomarkers?
Do vascular risk factors moderate AD?

5. **Progression:**
   a. Do VRF accelerate AD progression, independent of infarcts and hemorrhages?

6. **Mixed pathology:**
   a. How do we separate the effects of VRF on AD pathology versus on infarcts and hemorrhages?

7. **Multiple clinical phenotypes:**
   a. Will direct effects of VRF and AD biomarkers change clinical phenotype or just accelerate AD progression?
Do vascular risk factors moderate AD?

8. **Biomarkers**
   a. How are peripheral blood and CSF biomarkers related?
   b. Do cerebrovascular reactivity, endothelial, and blood brain barrier function mediate the relationship between VRF and AD?

9. **Risk factors**
   a. Are HTN, DM, DL risk factors for AD?

10. **Translational potential**
    a. Will decreased VRF decrease AD?
Systems Biology Approach to Complex Genetic-Environmental disease:
(General theory with “Koch’s” Postulates = special theory)

Diabetic Microvascular-Complication Network
EGFR-Induced Insulin Resistance and Impaired GAPDH-Induced Microvascular Complications

Conclusions: Do VRF moderate AD?

• Traditional reductionist approach using biomarker defined AD is just beginning.
  – So far...
    ▪ HTN – limited evidence
    ▪ DM – negative evidence
    ▪ Lipids – some evidence

• Systems Biology Approach

  interactions between molecular drivers of metabolic disease and β-amyloid dysregulation.
Aging Brain Investigators
NIA P01-AG12435