USC ADRC

1. Clarify how vascular factors contribute to cognitive impairment alone or in combination with AD.

2. Promote clinical trials and translational research in memory and aging at USC.

3. Increase recruitment and retention into UDS of minority subjects from USC's LALES (Latino) and CHES (Chinese) projects and surrounding neighborhoods.

4. Continue active participation in national initiatives, including NACC, ADCS, ADNI, and GWAS.
Reducing Alzheimer and vascular Contributions to cognitive impairment
Diverse Populations

Chinese

Latino

USC
## Prevalence of Vascular Risk Factors among adults ≥ 50 years of age by race/ethnicity, Behavioral Risk Factor Surveillance System, 2001-2004

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>387,201</td>
<td>28,464</td>
<td>4,925</td>
<td>16,089</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12</td>
<td>23.9</td>
<td>14.2</td>
<td>20.1</td>
</tr>
<tr>
<td>Obese (%)</td>
<td>22.7</td>
<td>35.8</td>
<td>6.1</td>
<td>27.7</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>44.2</td>
<td>63.6</td>
<td>40.3</td>
<td>42.5</td>
</tr>
<tr>
<td>Hypercholesterolemia(%)</td>
<td>42.5</td>
<td>38.7</td>
<td>39.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>15.5</td>
<td>19.9</td>
<td>8</td>
<td>13.2</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td>38.8</td>
<td>30.1</td>
<td>22.2</td>
<td>30.3</td>
</tr>
</tbody>
</table>

Kaplan-Meier log-rank test for equality of developing dementia, stratified by diabetes mellitus (DM) and the APOE ε4 allele $X^2 = 64.9$ (P<.001) Cardiovascular Health Study (n=2,547)

Swedish Twin Study
Margaret Gatz

Diabetes before age 65 is risk factor for dementia (vascular > Alzheimer).

<table>
<thead>
<tr>
<th>Diabetes status</th>
<th>Subjects (n)</th>
<th>All dementia</th>
<th>Alzheimer’s disease</th>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>12,296</td>
<td>498; 1.00 (reference); 1.00 (reference)</td>
<td>296; 1.00 (reference); 1.00 (reference)</td>
<td>74; 1.00 (reference); 1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1,396</td>
<td>139; 2.45 (1.97–3.03)*; 1.89 (1.51–2.38)†</td>
<td>56; 2.03 (1.47–2.80)*; 1.69 (1.16–2.36)†</td>
<td>31; 3.60 (2.33–5.57)*; 2.17 (1.36–3.47)†</td>
</tr>
<tr>
<td>Age of diabetes onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>643</td>
<td>48; 2.95 (2.14–4.08)*; 2.76 (1.97–3.87)†</td>
<td>16; 2.32 (1.37–3.94)*; 2.25 (1.29–3.92)†</td>
<td>12; 4.94 (2.61–9.35)*; 3.94 (1.90–8.15)†</td>
</tr>
<tr>
<td>≥65 years</td>
<td>753</td>
<td>91; 2.12 (1.64–2.75)*; 1.63 (1.23–2.16)†</td>
<td>40; 1.88 (1.29–2.74)*; 1.56 (1.05–2.32)†</td>
<td>18; 2.90 (1.70–4.94)*; 1.62 (0.92–2.80)†</td>
</tr>
</tbody>
</table>

Data are n; OR (95% CI) or OR (95% CI). *Adjusted for age, sex, and education. †Adjusted for age, sex, education, stroke, heart disease, hypertension, and BMI.

Xu W et al. Diabetes 2009;58:71-7
## Vascular Factors Increase Risk of Cognitive Impairment

### Vascular Factors

- Diabetes Mellitus
- Hyperlipidemia
- Hypertension
- Atherosclerosis
- Amyloid angiopathy

### Mechanism?

- Ischemic infarction
  - Strokes (symptomatic infarcts)
  - Microinfarcts
- Increase AD pathology?
  - Plaques and tangles
- Metabolic dysfunction?
  - Mitochondria
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Program Project (Chui): The Aging Brain (USC, UCD, UCSF, UCLA, UCB)
ADRC Project 1 (Zelinski): The Course of Cognitive Change in Late Life

Vascular Risk Factors

Carotid-IMT Retinal-AVR

Direct Effects?

Beta-amyloid Tauopathy

Hippocampus

△ CGM

△ Exec

Infarcts Hemorrhages

WMH Incident Infarcts

Clinical Psych MRI PIB Path
Infarcts on MRI for VCI     Amyloid PET for AD

Rabinovici GC. Presented at Human Amyloid Meeting, Toronto, 2010
Aging Brain Program Project: USC, UCD, Berkeley, UCSF, UCLA
Project 1: Zelinski

The course of cognitive change in late adulthood

- The goal of this project is to combine the extensive psychometric longitudinal data obtained for up to 15 years from participants in the Long Beach Longitudinal Study (LBLS), a group of initially healthy adults,

- With vascular and brain structure measures collected at two time points three years apart to test hypotheses about vascular and AD correlates of the development of cognitive declines.
1. Clarify how vascular factors contribute to cognitive impairment alone or in combination with AD.
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USC Atherosclerosis Clinical Trials
Howard Hodis & Wendy Mack

- **Estrogen** in the Prevention of Atherosclerosis Trial (NIH AG-18798):
  - 43% ethnic minority, 21% Latino.

- Women’s **Estrogen-Progestin** Lipid-Lowering Atherosclerosis Trial (NIH HL-49298):
  - 69% ethnic minority, 44% Latino.

- **Troglitazone** Atherosclerosis Regression Trial (Parke-Davis):
  - 89% Latino

- **B-Vitamin** Atherosclerosis Intervention Trial (NIH AG-17160):
  - 35% ethnic minority, 11% Latino

- **Vitamin E** Atherosclerosis Prevention Study (NIH AG-13860):
  - 26% ethnic minority

- Women’s **Isoflavone Soy** Health Trial (NIH AT-001653):
  - 37% ethnic minority, 16% Latino

- **Early-Late Intervention Trial of Estradiol** (NIH AG-024154):
  - 32% ethnic minority, 13% Latino.
ADRC Project 2: Brinton & Pike
Determine the efficacy of candidate NeurosERMs and NeurosARMs to:

- Induce markers of neuroprotection, neural defense, vascular viability and to modify AD pathology development *in vitro*.
- 1) reduce levels of tau phosphorylation and Aβ accumulation; 2) prevent cognitive deficits; 3) protect against vascular injury; and 4) prevent proliferation in reproductive tissues in the 3xTg-AD triple transgenic mouse model of Alzheimer’s pathology.
Estradiol-Induced Neuroprotective Signaling Pathways Converge on Mitochondria

Nilsen & Brinton, PNAS 2004; Mannella & Brinton J Neurosci 2006; Brinton TINS 2008
Estrogen Therapy Alternatives for the Brain

1997 – 2007 National Institute on Aging (2 PO1 AG14751)
Project 2 – Models of Estrogen Interactions with Alzheimer’s Disease, Finch PI

2003 – 2008 National Institute of Mental Health (R01 MH67159-01A1) Estrogen-Induced Neuroprotective Mitochondrial Mechanisms Brinton, PI

PhytoSERMs
Natural Source Estrogen Molecules
Nutraceutical Strategy
Dev 2-5 yrs

NeuroSERMs
Novel Designer Estrogen Molecules
Pharmaceutical Strategy
Dev 7-15 yrs

Zhao & Brinton, J. Medicinal Chemistry, 2006 & 2007
Allopregnanolone reverses neurogenic and cognitive deficits in mouse model of Alzheimer's disease

Information, appointments, research participation, and referrals call:

**USC Keck School of Medicine**  
Los Angeles, CA  
(323) 442-7600  
gsc@usc.edu

**Rancho Los Amigos National Rehabilitation Center**  
Downey, CA  
(562) 401-8130
Thank you!

USC ADRC Clinical Core