

# *McKNIGHT-NIA COGNITIVE SUMMIT*

*Associations of non-neurologic conditions  
with cognitive impairment and dementia --  
contributions of epidemiology and  
neuropathology*

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# Alternative endpoints for risk factor identification

- Cross-sectional associations with prevalent conditions (only valid for risk factors that definitely existed prior to development of the endpoint)
- Risk factors measured without bias prior to development of the endpoint -- generally a valid method
- Risk factors measured during life, correlated with specific lesions identified at autopsy

# The Honolulu-Asia Aging Study

- Started as the Honolulu Heart Program in 1965.  
N=8006 Japanese-American men born 1900-1919
- HAAS established 1991-93, 3734 examined for cognitive and motor function, dementia, stroke, and Parkinson's disease at 2-3 year intervals
- Autopsies on ~ 35% of demented and 17% of non-demented decedent participants

# Cross-sectional associations of selected "risk factors" with CASI score (baseline exam, 1991-93)

*N= 3560 Controlling for education, apoE4 zygosity, and age.  
Separate regression models for each risk factor.*

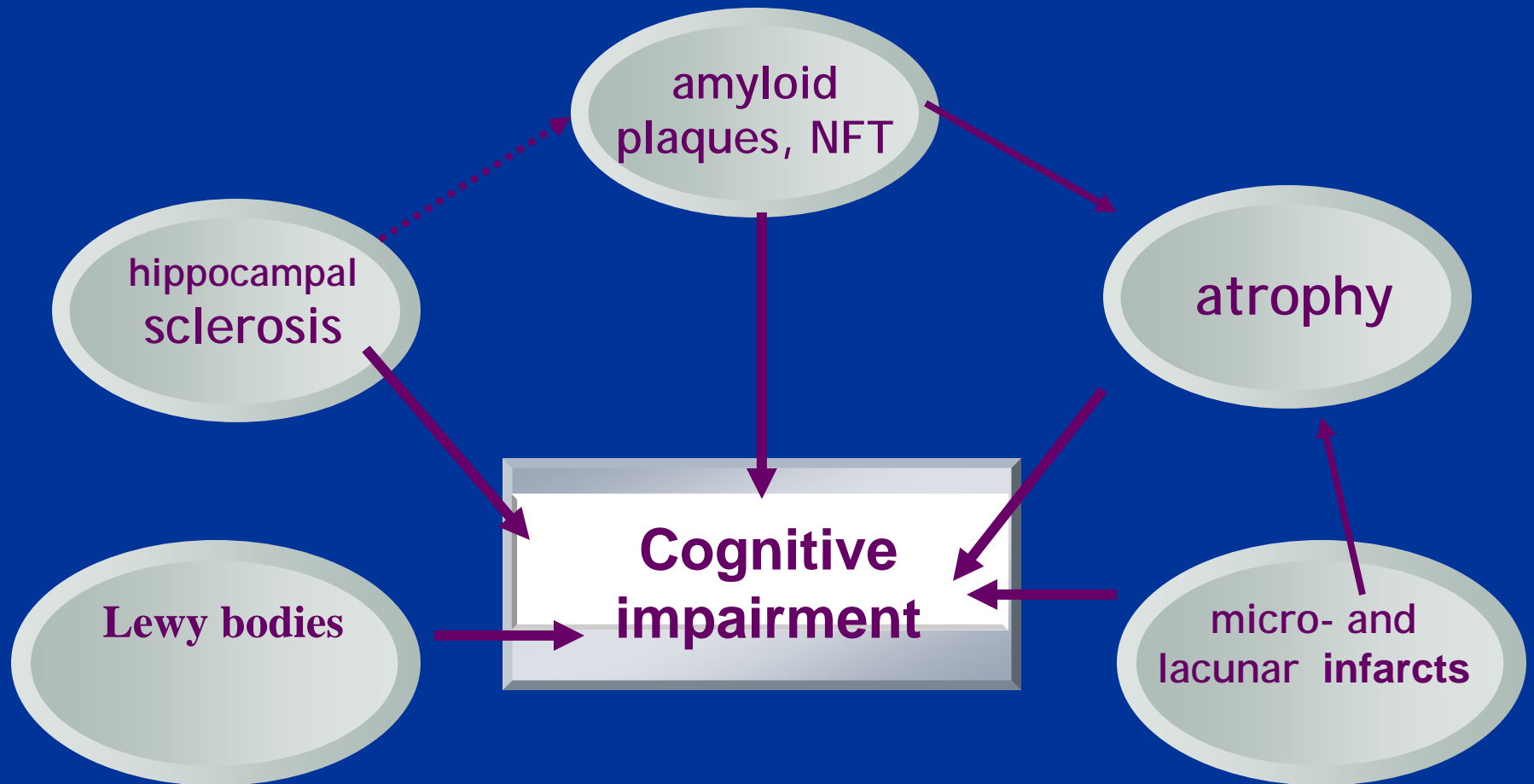
<u><i>Risk factor</i></u>	<u><i>R<sup>2</sup></i></u>	<u><i>p</i></u>
<i>Heart disease</i>	-	<i>n.s.</i>
<i>Fasting insulin (inverse)</i>	<i>0.3 %</i>	<i>0.0003</i>
<i>Fasting glucose</i>	-	<i>n.s.</i>
<i>HDL-C (direct)</i>	<i>0.3 %</i>	<i>&lt;0.0001</i>
<i>Serum Testosterone (direct)</i>	<i>0.4 %</i>	<i>&lt;0.0001</i>
<i>Serum Estrogen (inverse)</i>	<i>0.5 %</i>	<i>&lt;0.0001</i>
<i>Sleepy throughout day (inverse)</i>	<i>1.2 %</i>	<i>&lt;0.0001</i>

**Associations of selected baseline risk factors  
among 1626 men with baseline CASI scores  $\geq 74$   
with CASI scores 6 years later (1997-99)**

*Controlling for education, apoE4 zygosity, age, and baseline CASI; separate regression models for each risk factor*

<u><i>Risk factor</i></u>	<u><i>R<sup>2</sup></i></u>	<u><i>p</i></u>
<i>Heart disease (inverse)</i>	<i>0.3 %</i>	<i>0.003</i>
<i>Fasting insulin</i>	<i>-</i>	<i>n.s</i>
<i>Fasting glucose</i>	<i>-</i>	<i>n.s.</i>
<i>HDL-C</i>	<i>-</i>	<i>n.s</i>
<i>Serum Testosterone</i>	<i>-</i>	<i>n.s</i>
<i>Serum Estrogen (inverse)</i>	<i>0.2 %</i>	<i>0.03</i>
<i>Sleepy throughout day (inverse)</i>	<i>0.5 %</i>	<i>0.0004</i>

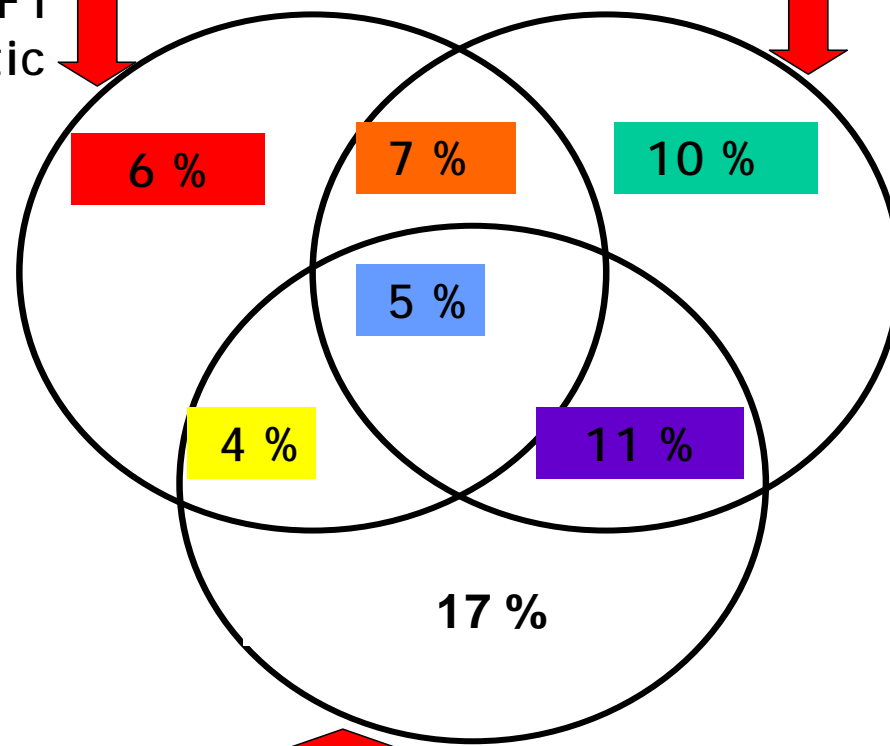
*In the HAAS, at least 5 types of brain lesion are independently and commonly associated with cognitive impairment and dementia*



# Overlapping occurrence of Alzheimer lesions, microvascular infarcts, and atrophy in 485 autopsied HAAS decedents

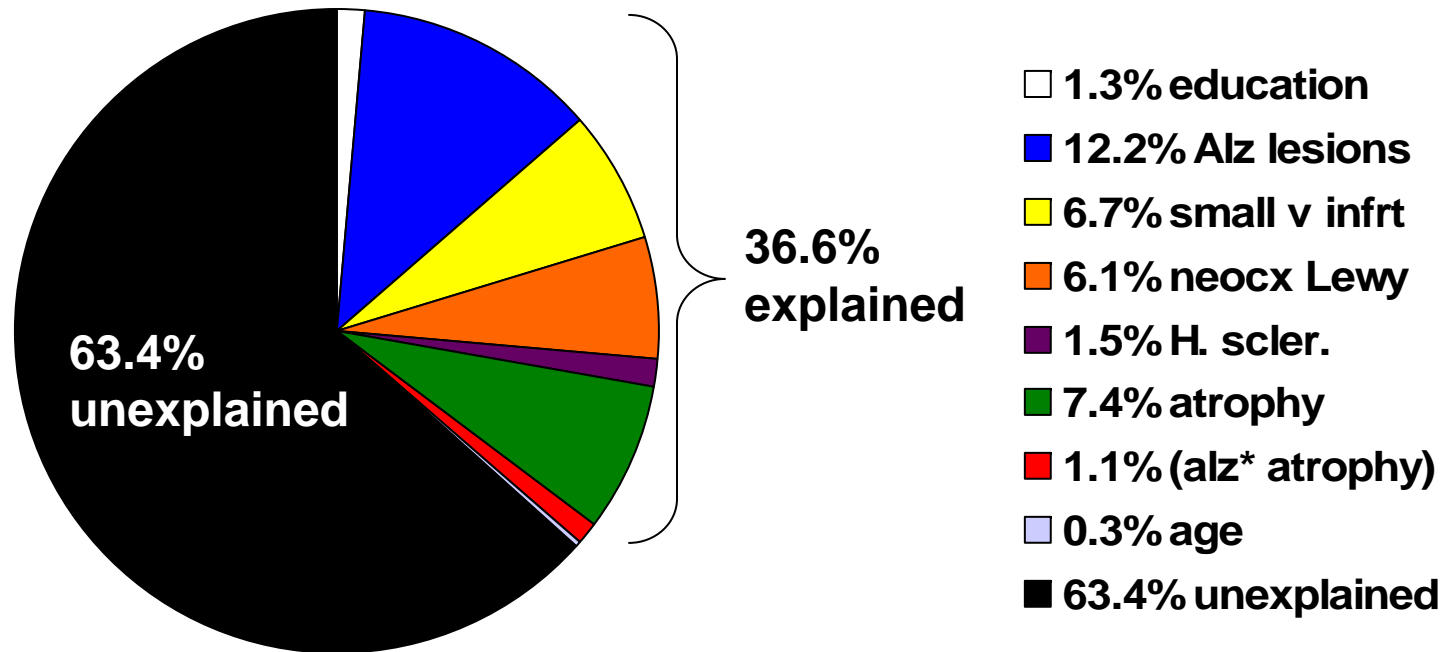
High counts of neocortical NFT and/or neuritic plaques

Atrophy (>12%)



some/many microinfarcts and lacunar infarcts

# Analysis of Variance in Last Cognitive Test Score



## Associations of selected baseline risk factors with neocortical neurofibrillary tangle count at autopsy

**N >= 407**    *Controlling for apoE4 zygosity and age at death*  
*Separate regression models for each risk factor*

<u>Risk factor</u>	<u>chi<sup>2</sup></u>	<u>p</u>
<i>Heart disease</i>	<i>0.28</i>	<i>n.s.</i>
<i>Fasting insulin</i>	<i>1.02</i>	<i>n.s.</i>
<i>Fasting glucose (inverse)</i>	<i>3.96</i>	<i>0.05</i>
<i>HDL-C (direct)</i>	<i>6.45</i>	<i>0.01</i>
<i>Serum Testosterone</i>	<i>0.04</i>	<i>n.s.</i>
<i>Serum Estrogen</i>	<i>0.30</i>	<i>n.s.</i>
<i>Sleepy throughout day (direct)</i>	<i>3.69</i>	<i>0.05</i>

## Associations of selected baseline risk factors with total microinfarct count at autopsy

**N >= 407**    *Controlling for apoE4 zygosity and age at death*  
*Separate regression models for each risk factor*

<u>Risk factor</u>	<u>chi<sup>2</sup></u>	<u>p</u>
<i>Heart disease</i>	<i>2.58</i>	<i>0.11</i>
<i>Fasting insulin</i>	<i>0.45</i>	<i>n.s</i>
<i>Fasting glucose (direct)</i>	<i>3.11</i>	<i>0.08</i>
<i>HDL-C (inverse)</i>	<i>11.8</i>	<i>0.0006</i>
<i>Serum Testosterone</i>	<i>1.60</i>	<i>n.s</i>
<i>Serum Estrogen</i>	<i>2.38</i>	<i>n.s.</i>
<i>Sleepy throughout day (direct)</i>	<i>0.07</i>	<i>n.s</i>

## Associations of selected baseline risk factors with general brain atrophy at autopsy

**N >= 407**    *Controlling for apoE4 zygosity and age at death*  
*Separate regression models for each risk factor*

<u>Risk factor</u>	<u>R<sup>2</sup></u>	<u>p</u>
<i>Heart disease</i>	<i>&lt;0.01 %</i>	<i>n.s</i>
<i>Fasting insulin</i>	<i>0.01 %</i>	<i>n.s</i>
<i>Fasting glucose (direct)</i>	<i>0.54 %</i>	<i>0.10</i>
<i>HDL-C (inverse)</i>	<i>0.63 %</i>	<i>0.08</i>
<i>Serum Testosterone (direct)</i>	<i>0.63 %</i>	<i>0.09</i>
<i>Serum Estrogen</i>	<i>&lt;0.01 %</i>	<i>n.s.</i>
<i>Sleepy throughout day (direct)</i>	<i>0.07 %</i>	<i>0.07</i>

## Associations of selected baseline risk factors with brainstem Lewy bodies at autopsy

**N >= 407**    *Controlling for apoE4 zygosity and age at death*  
*Separate regression models for each risk factor*

<u>Risk factor</u>	<u>chi<sup>2</sup></u>	<u>p</u>
<i>Heart disease</i>	<i>0.76</i>	<i>n.s.</i>
<i>Fasting insulin</i>	<i>0.42</i>	<i>n.s.</i>
<i>Fasting glucose</i>	<i>1.24</i>	<i>n.s.</i>
<i>HDL-C</i>	<i>0.47</i>	<i>n.s.</i>
<i>Serum Testosterone</i>	<i>1.51</i>	<i>n.s.</i>
<i>Serum Estrogen</i>	<i>0.05</i>	<i>n.s.</i>
<i>Sleepy throughout day</i>	<i>0.40</i>	<i>n.s.</i>

# Conclusions -- 1

- Except for conditions (risk factors) known to have existed prior to cognitive decline, cross-sectional associations cannot reliably identify true risk factors
- Risk factors predicting future cognitive impairment are likely to be valid when they were measured without bias prior to cognitive decline

## Conclusions -- 2

- Cognitive impairment in late life can be due to any one or a combination of several different pathologic processes indicated by different lesions
- Different risk factors may influence different pathologic processes
- A more precise linkage of specific risk factors with specific pathogenic processes will further our understanding of the pathogenesis of cognitive decline, and improve the efficiency of our research toward effective prevention strategies

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