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

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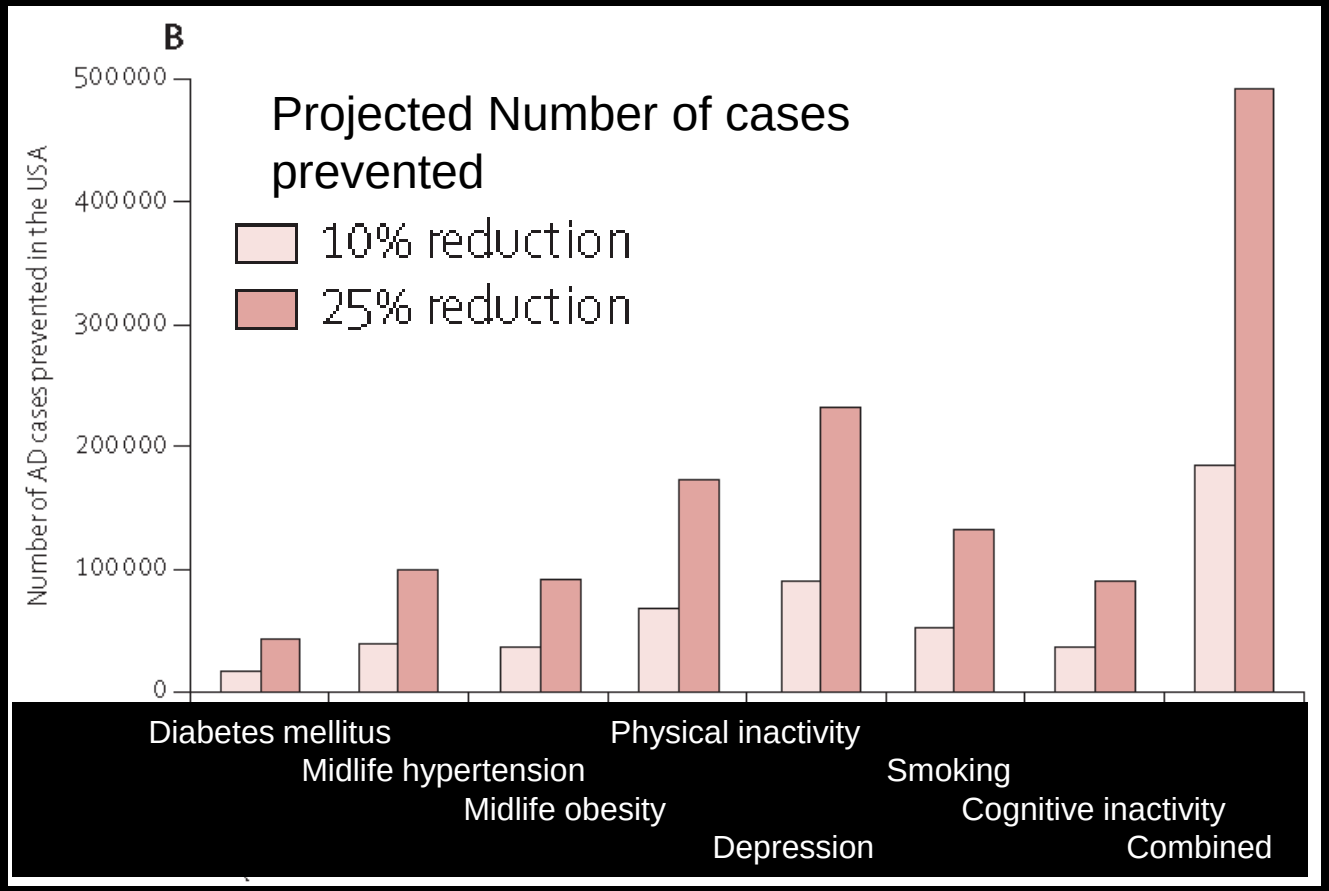
Introduction

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”



Barnes DE and Yaffe K. Lancet Neurology 2011; 10: 819.

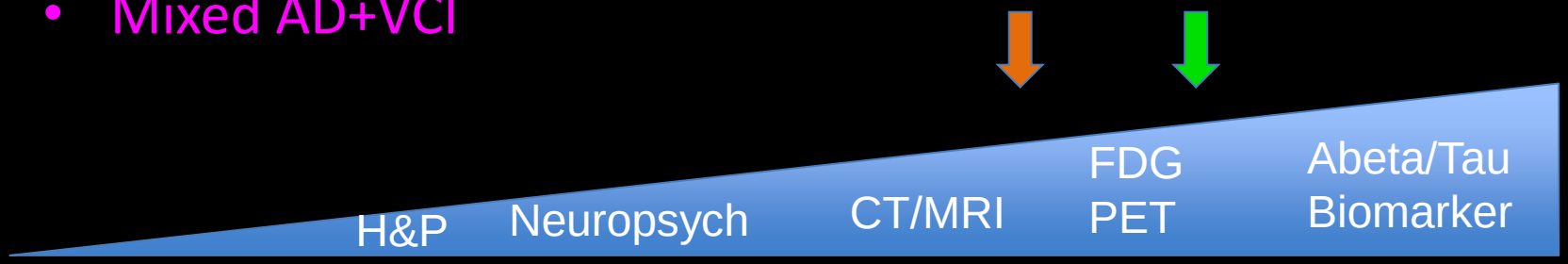
What do we mean by "AD"?
AD = Biomarker Standard

Do Not Mean

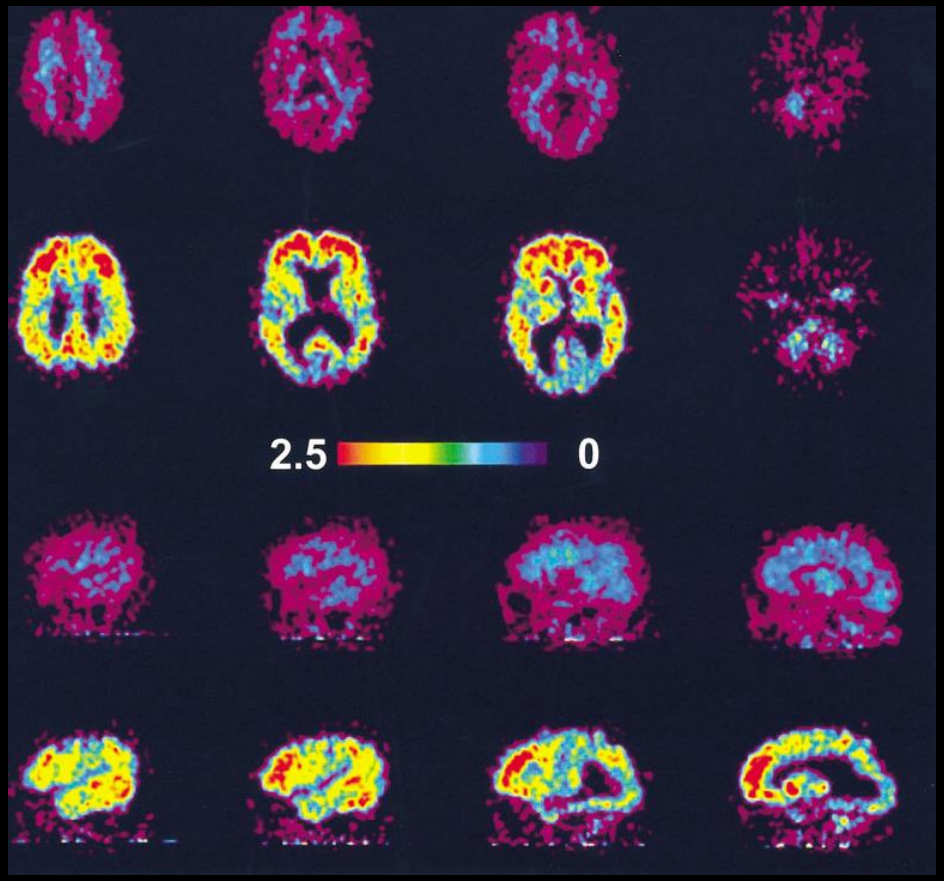
- "AD" defined as progressive dementia without clinical evidence of stroke (defined solely based on history, exam, neuropsychology, or structural MRI/CT).
- Mixed AD+VCI

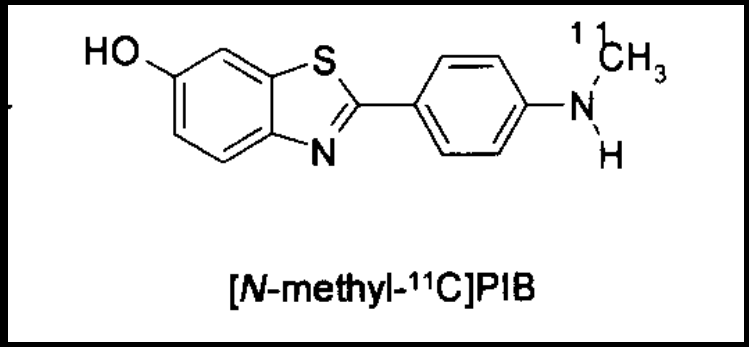
Do Mean

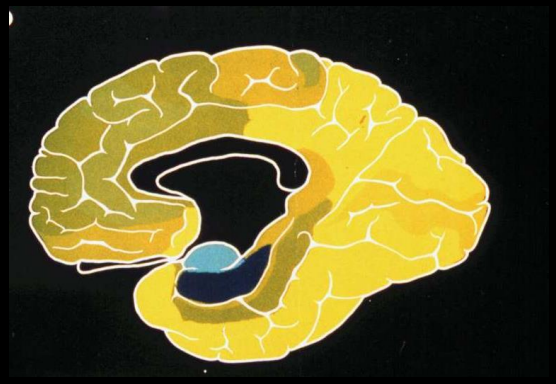
- **AD** defined by widespread beta-amyloid plaques and p-Tau neurofibrillary tangles.
  - Beta-amyloid by CSF, PET, or neuropathology
  - P-Tau by CSF, PET or neuropathology



2004: Imaging β-Amyloid during life with Pittsburgh Compound B (PIB)

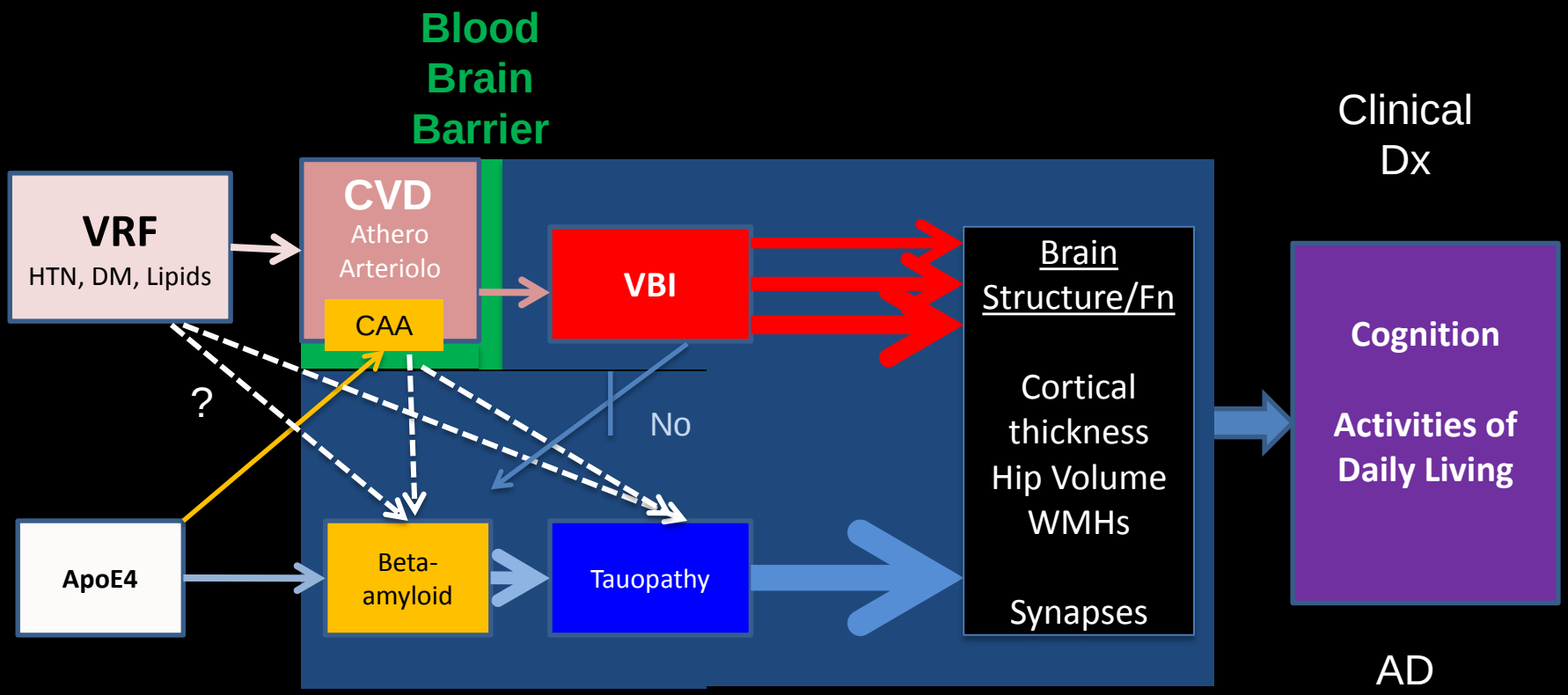






Klunk W. Ann Neurol 2004; 55: 306-319.

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



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

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

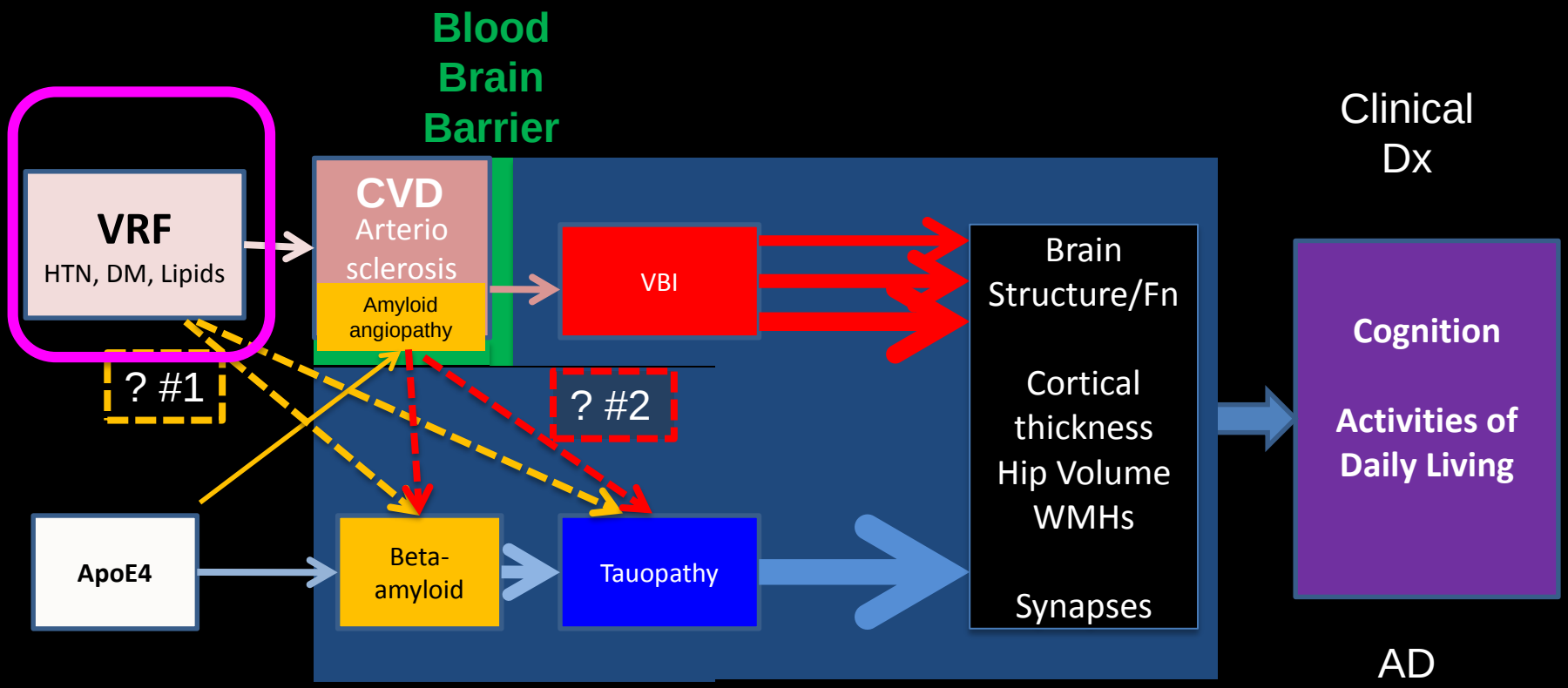
Topic 5 - Vascular Contributions to ADRD: Focus on …….AD/Vascular Interactions

Focus Area 2: Human-Based Studies

Recommendation 2 (S Craft / H Chui):

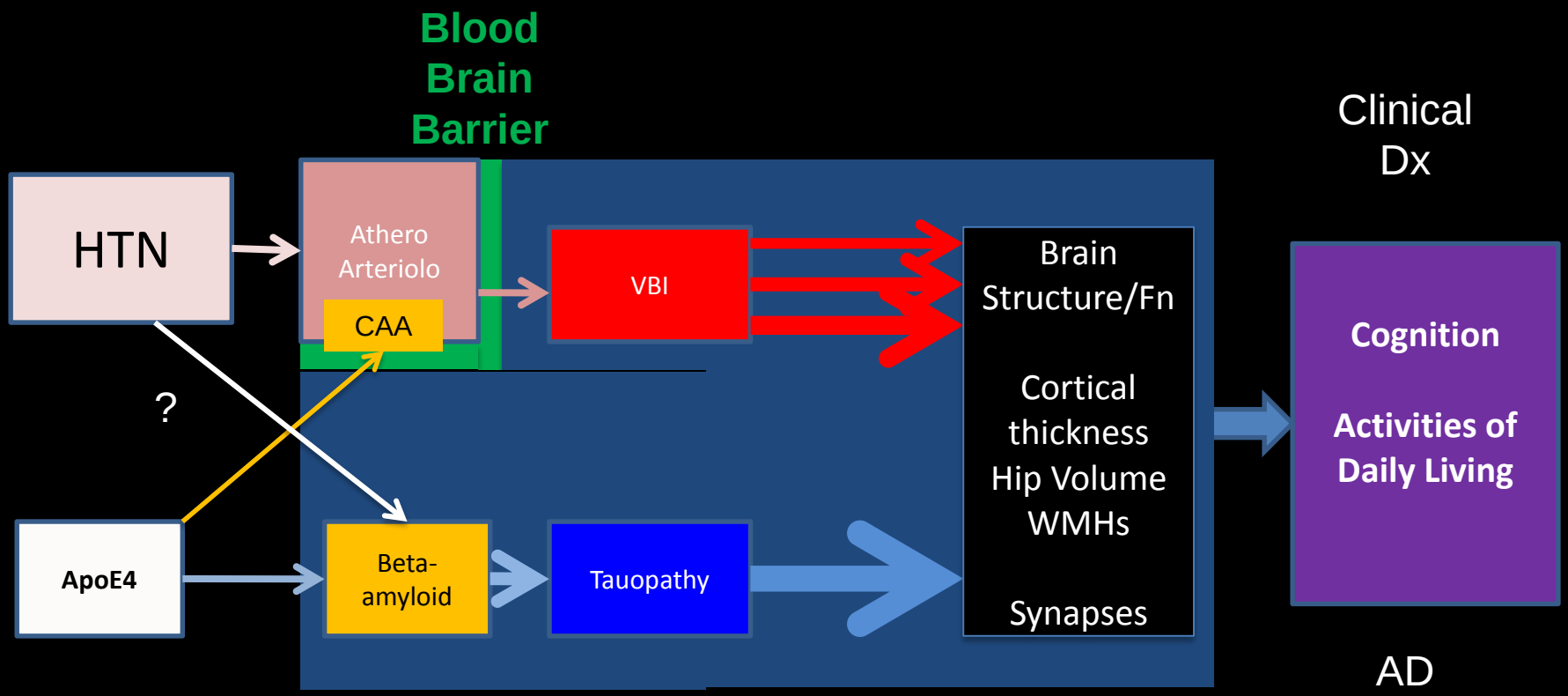
5.2.2. Determine interrelationships among cerebrovascular disease (CVD), vascular risk factors (VRF) with Aβ & neurodegeneration.

Associations Between VRF and AD
#1 Traditional approach
VRF and AD; CVD and AD
#3 System-based approach



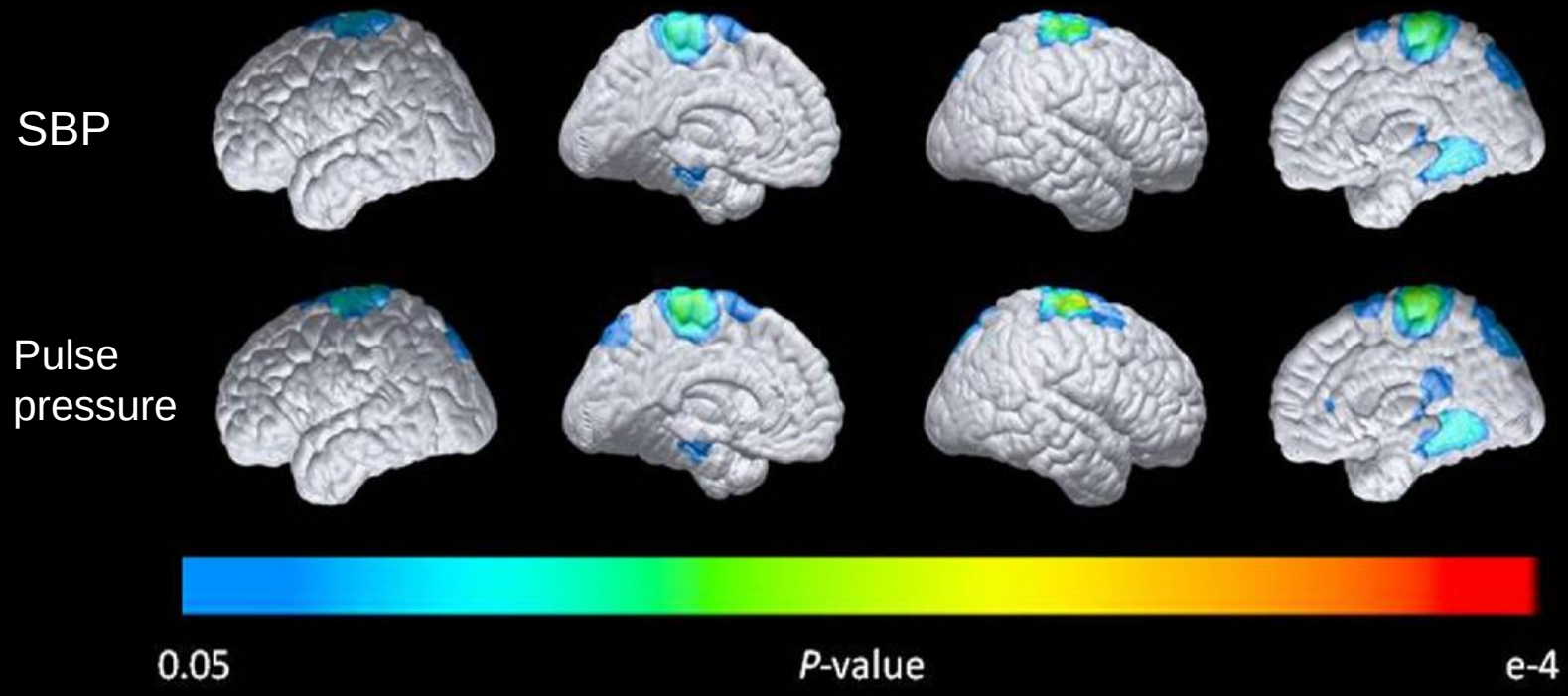
AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts

Associations Between HTN and AD: Parallel or Interactive pathways?



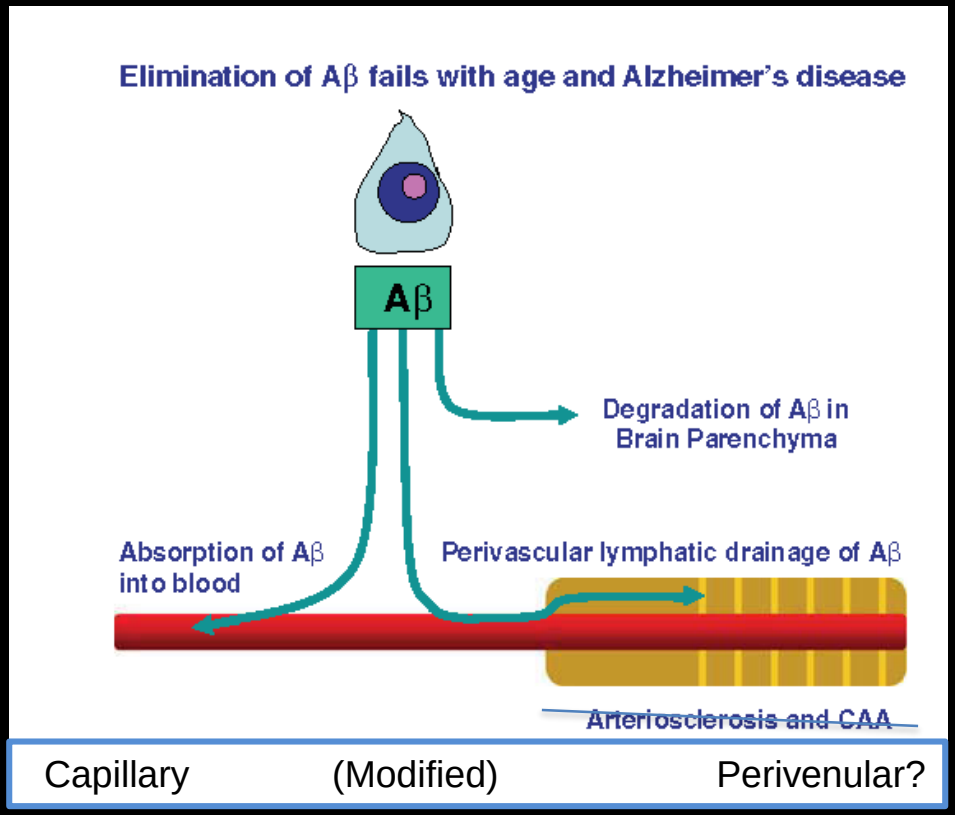
AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts

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

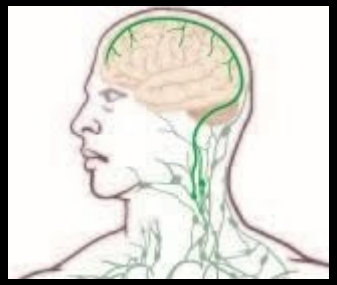


Weller R et al Acta Neuropath 2009; 117:1-14.

Enzymatic degradation by
Neprilysin
Insulin-degrading enzyme

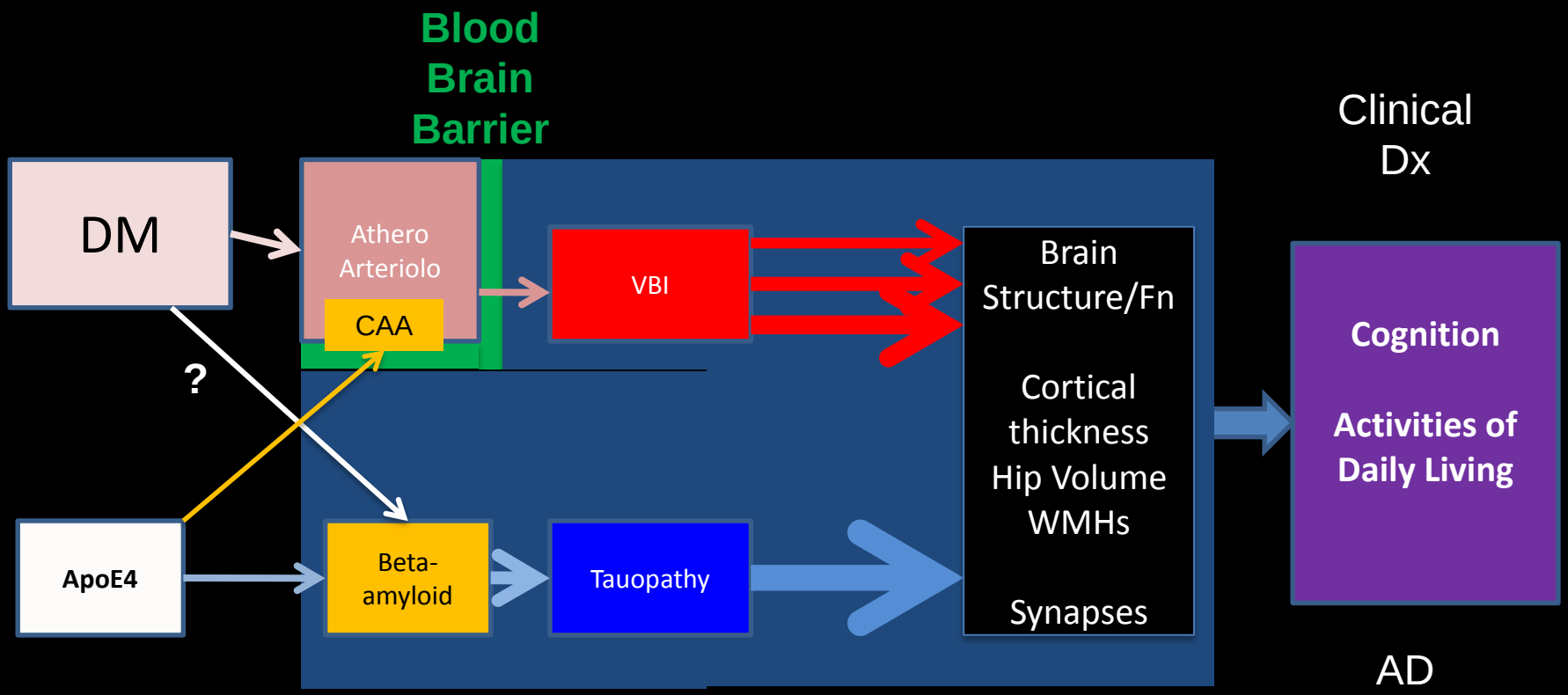
Blood clearance via LRP-1
(low density lipoprotein receptor-related protein) is less efficient with apolipoprotein E4

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”

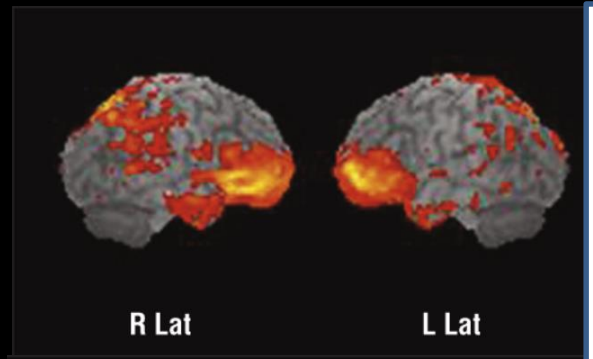
Study	Age (yr)	F/U (yr)	Numbers DM	Numbers No DM	All dementia	Vascular dementia	AD+VaD	Alzheimer disease
Yoshitake 1995 **Hisayama 1**985-1992	>65	7	70	756		**2.8** (2.6, 3.0)		**2.2** (0.97, 4.9)
Ott 1999 **Rotterdam**1990-1994	>55	2.1	692	5678	1.9 (1.3, 2.8)	**2.0** (0.7, 5.6)	3.0 (1.0,9.3)	**1.8** (1.1, 3.0)
Luchsinger 2001 **WHICAP** 1992-1997	≥65	4.3	255	1007		**3.4** (1.7, 6.9)		**1.3** (0.8,1.9)
MacKnight 2002 **CSHA**	≥65	4-6	503	5071	1.26 (0.9,1.7)	**2.03** (1.15, 3.5)		**1.3** (0.83, 2.1)
Peila 2002 **HAAS** 1991-1996	72-93	2.9	900	1674	1.5 (1.0, 2.2)	**2.3** (1.1, 5.0)	1.8 (1.1, 2.9)	1.6 (0.9, 3.0)
Cheng 2011 **WHICAP** 1999-2001	>65				1.7 (1.4, 2.90)		1.6 (1.0, 2.6)	**1.3** (0.8, 2.2)
Arvanitakis 2004 **Religious Orders Study**	75	5.5	127	697				**1.6** (1.1, 2.5)
Ahtilouoto 2010 **Vantaa 85+**	>85		87	268	2.09 (1.34, 3.25)			

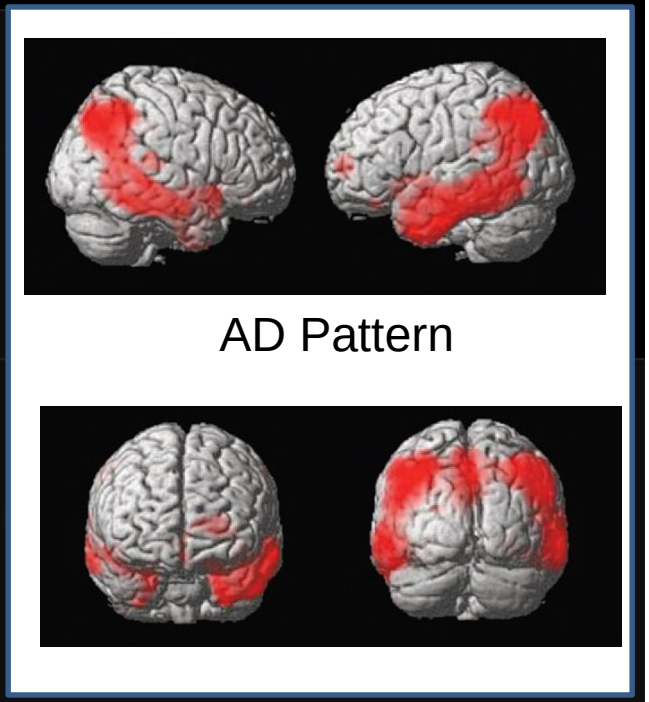
Diabetes is associated with infarction but not AD Pathology Religious Orders Study (n=200)

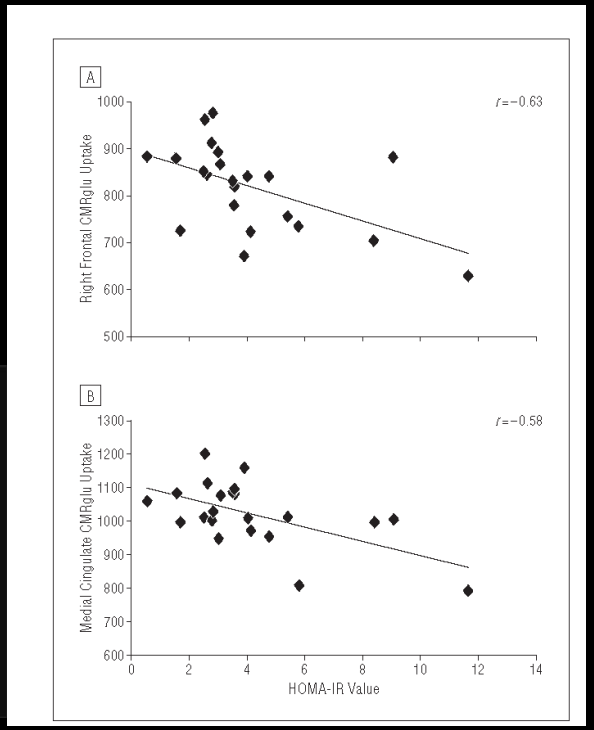
Characteristic	Diabetes (n= 36)	Non diabetes (n=197)	P Value
Age at death	84.4 (6.6)	85.8 (6.7)	0.25
Sex, % men	63.9	42.1	0.02
Education, y	17.4 (4.1)	18.2 (3.4)	0.22
Dementia, %	50.0	44.2	0.52
Cerebral Infarction	52.8	32.5	0.02
Cortical infarction	19.4	8.1	0.06
Subcortical infarction	50	26.9	0.01
Overall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

Arvanitakis Z et al. Neurology 2006;67:1960–1965

Regional pattern of glucose hypmetabolism differs in T2DM and AD





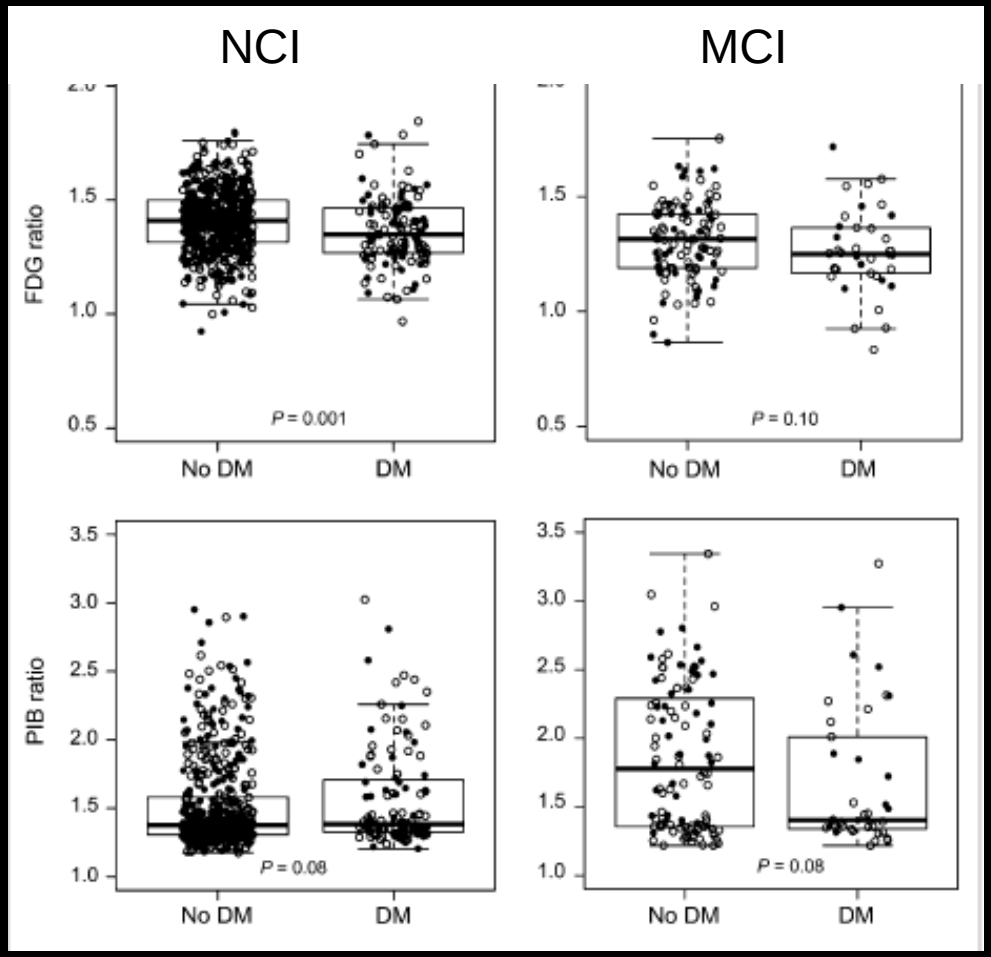


Baker L.. Craft S. *Arch Neurol. 2011;68(1):51-57*

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

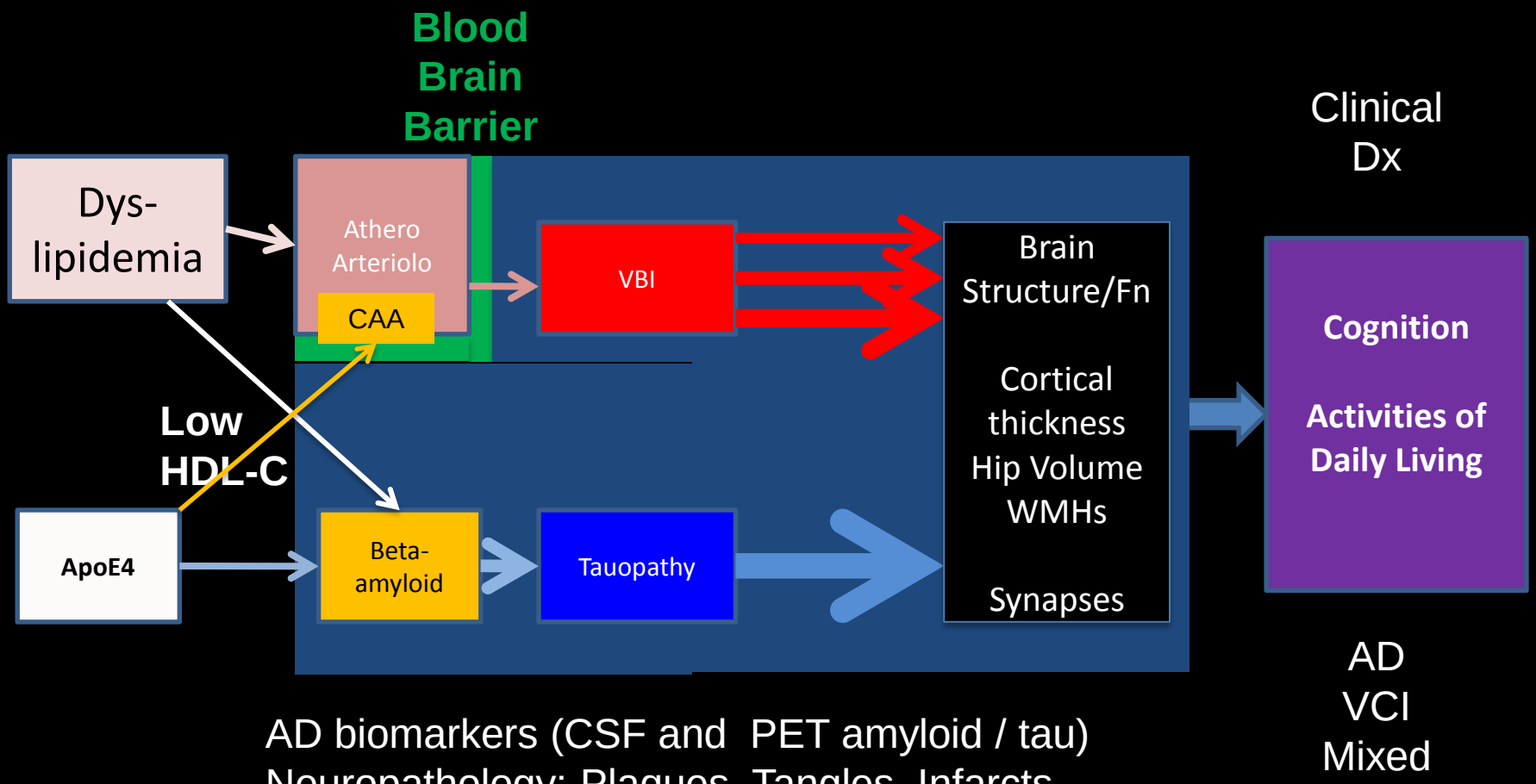
FDG PET

PiB ratio



Roberts R. J Nucl Med 2014; 55:759–764

Associations Between Lipids and AD: Parallel or Interactive pathways?



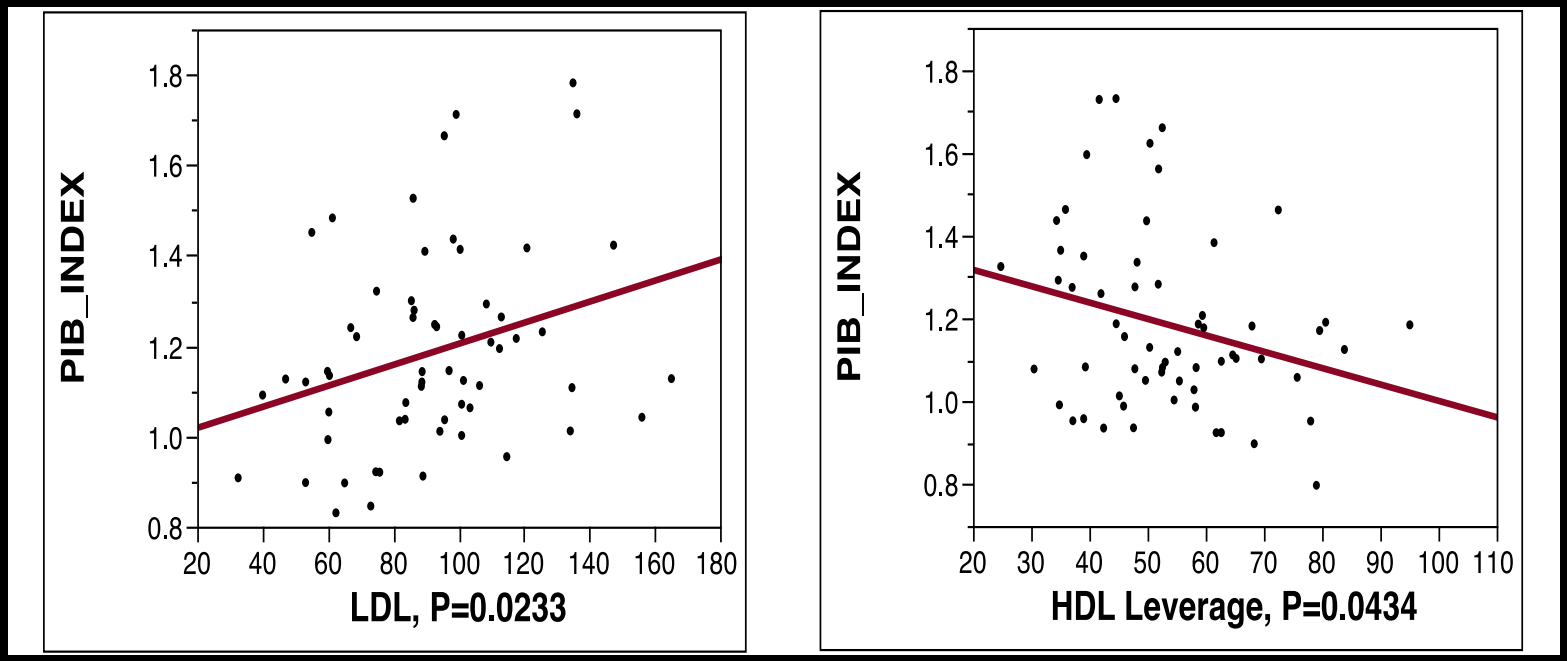
Washington Heights Inwood Columbia Aging Project (WHICAP)

- 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).

Luchsinger JA et al. Neurology 2005; 65: 545-551.

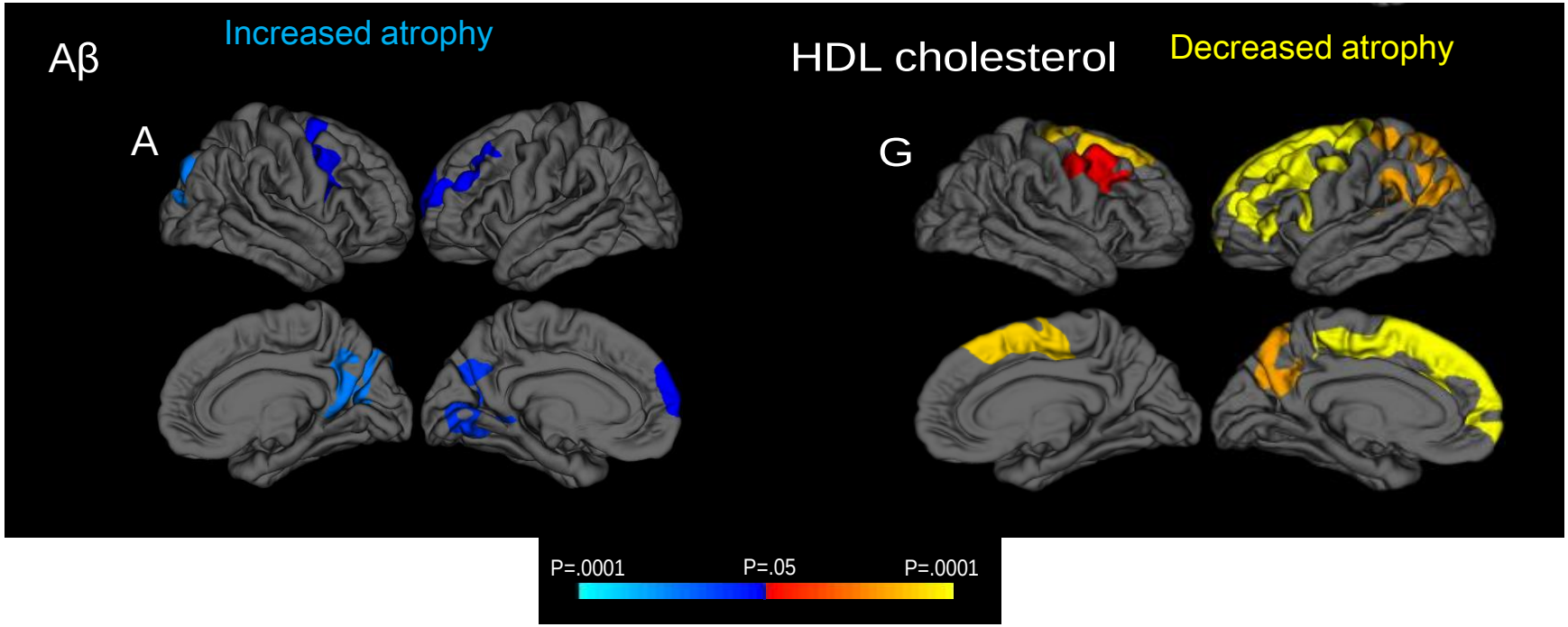
LDL-Cholesterol is associated with increased; while HDL cholesterol is associated with decreased brain amyloid



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

Reed BR et al. JAMA Neurology 2014; 71: 195-200.

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



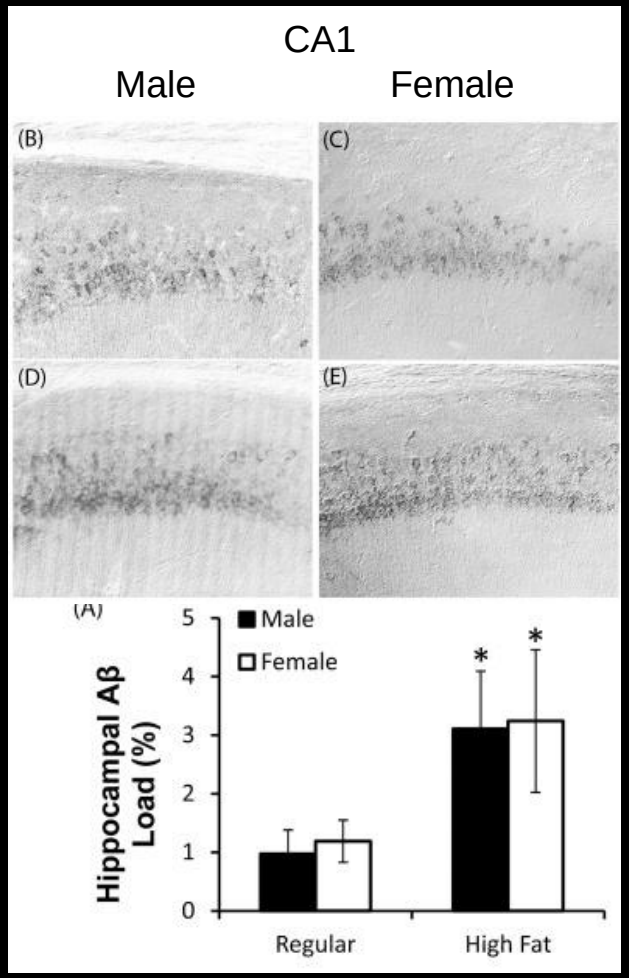
Aβ = -.14 (p= .07); HDL = +.45 (p<.01); Interaction = +.36 (p = .01)

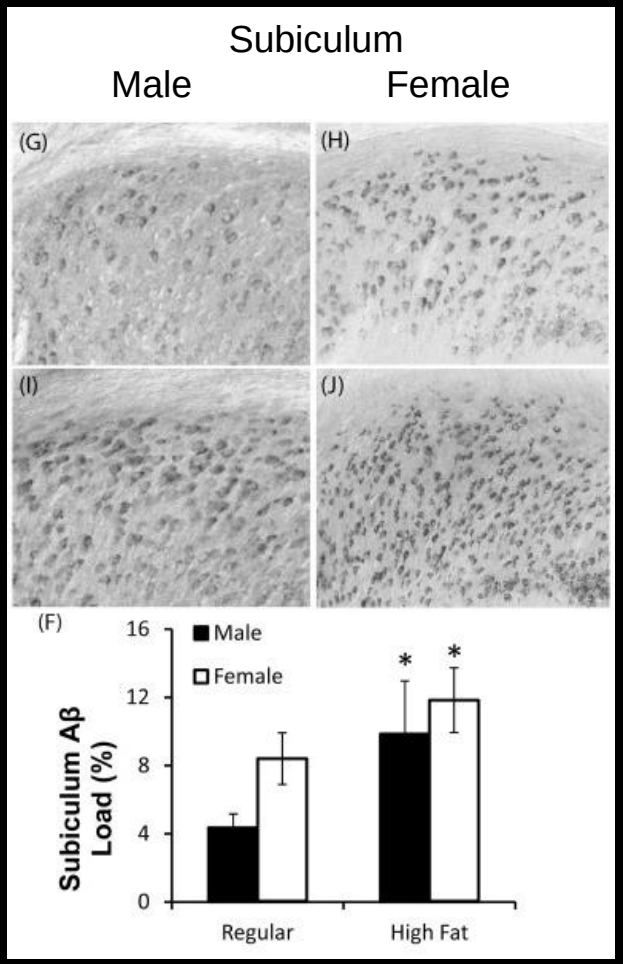
Villeneuve S, et al., Neurology 2014; 83: 40-7

Increased accumulation of hippocampal β-amyloid in both male and female 3xTg Mice fed a high fat diet

Regular diet
(14% kCal = fat)

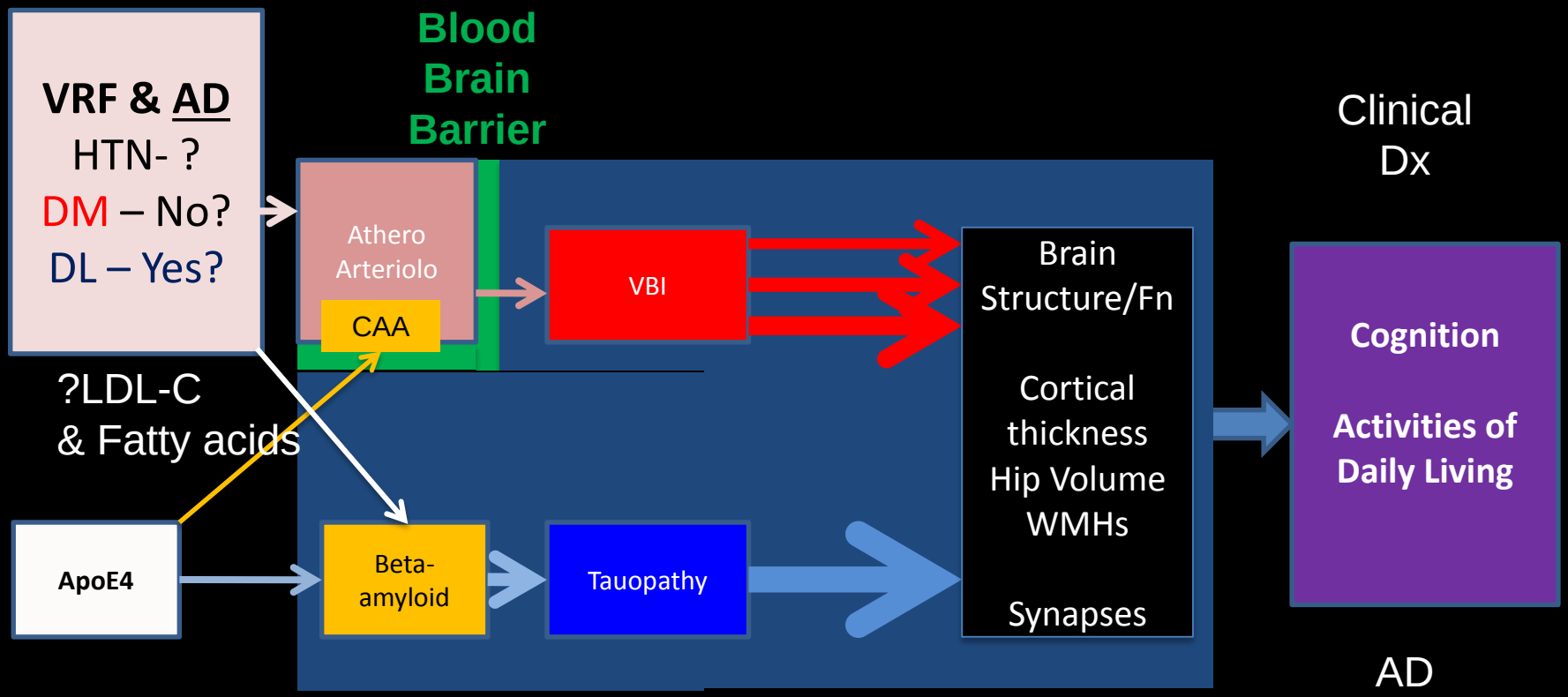
High fat diet
(60%kCal = fat)





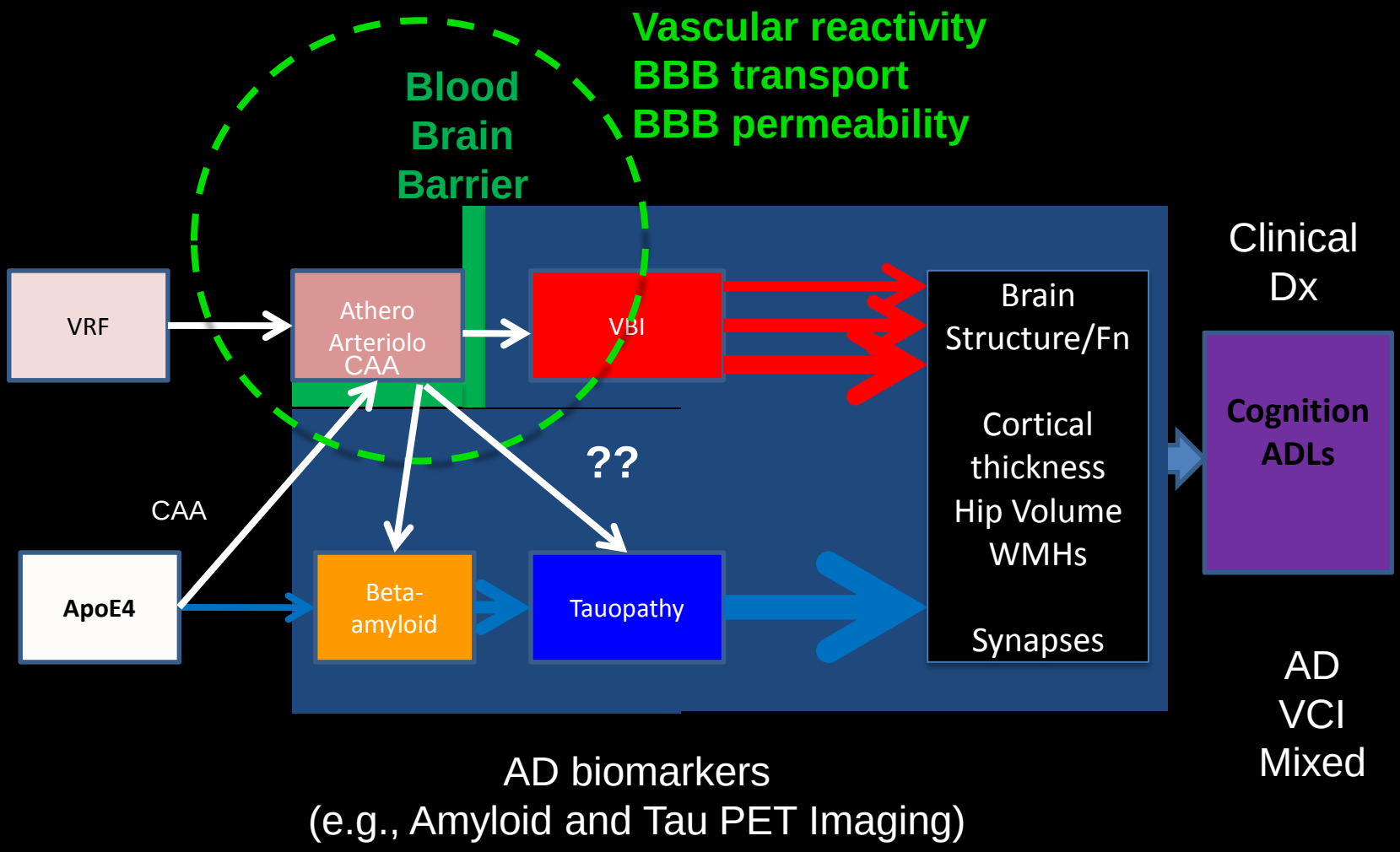
Barron AM…. Pike D. PLoS One 2013;8:e78554.

Associations Between VRFs and AD: Parallel or Interactive pathways?



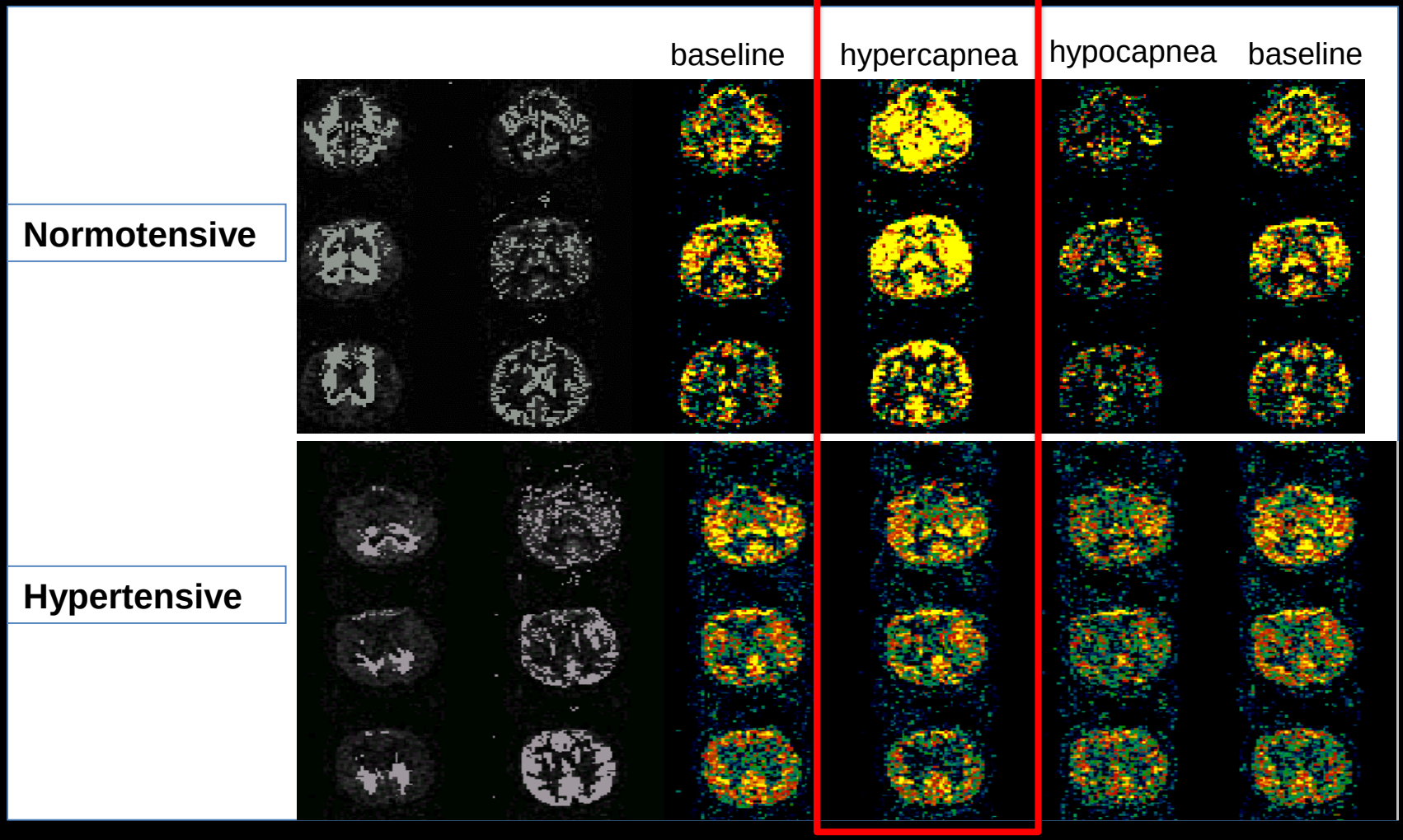
AD biomarkers (CSF and PET amyloid / tau)
Neuropathology: Plaques, Tangles, Infarcts

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



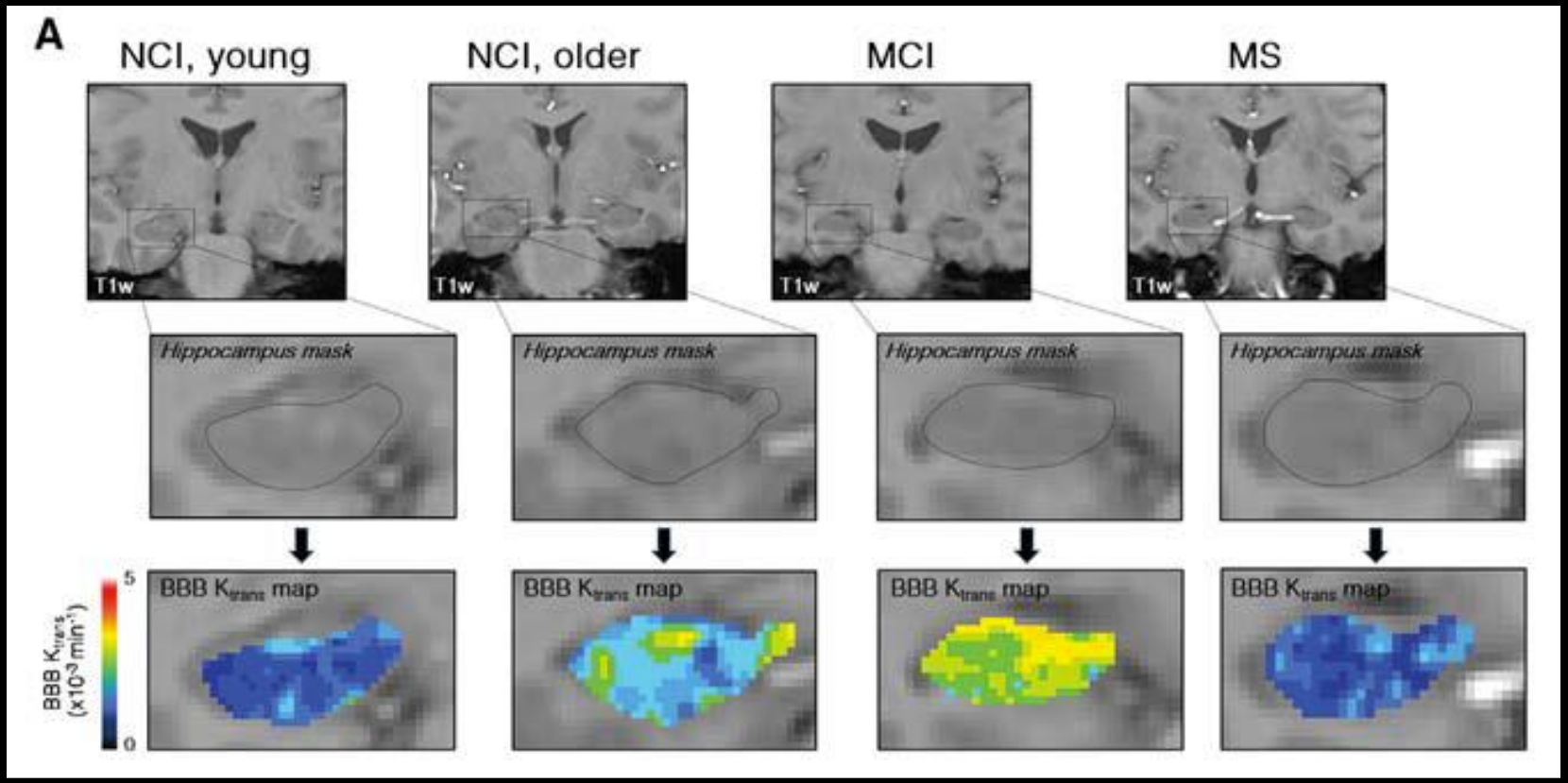
Hypertension-Associated Impairment in Vasoreactivity to Hyper- and Hypo-Capnea (pCO_2)

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



Montagne A et al., Neuron 2015; 85: 296-302.

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?

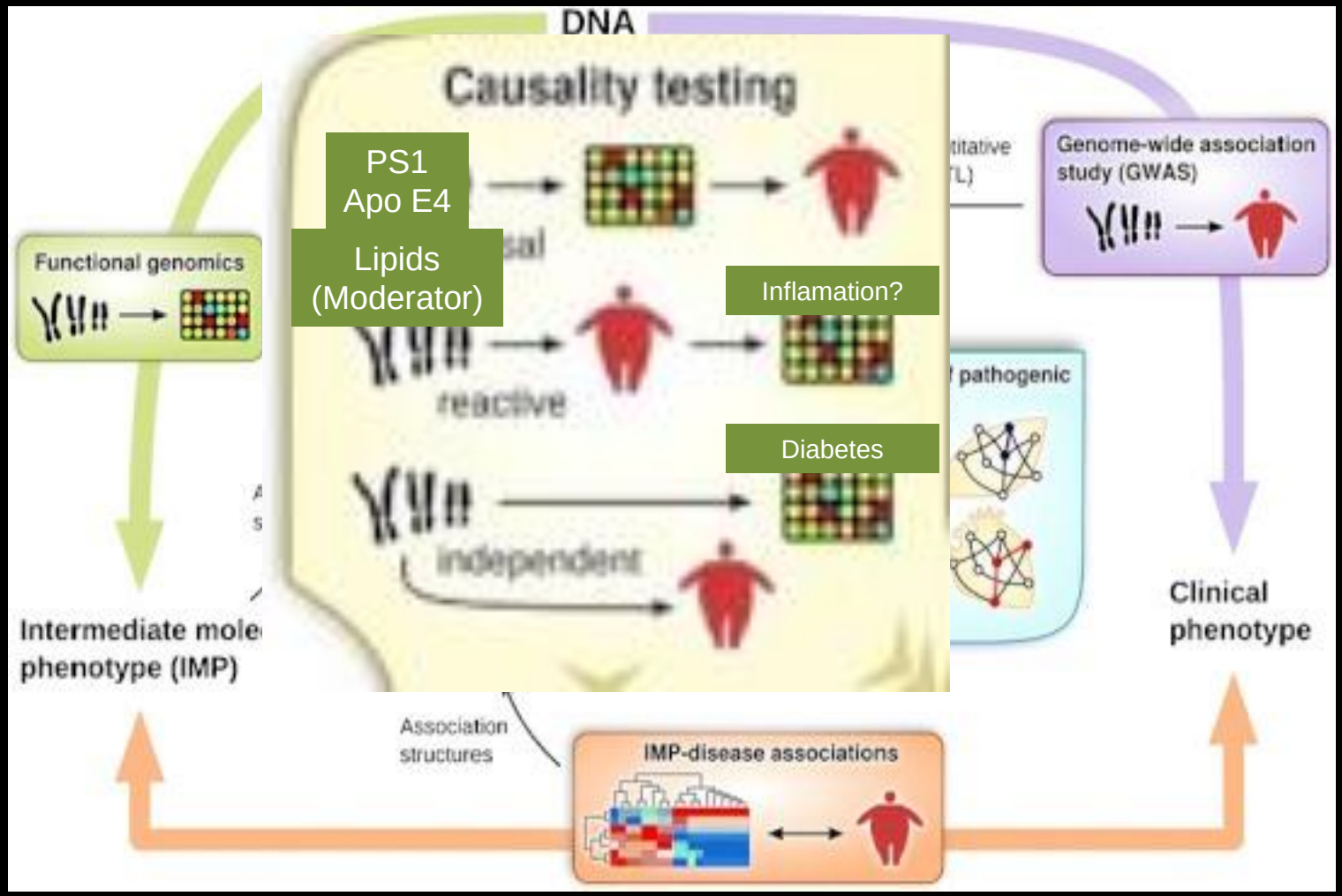
Do vascular risk factors moderate AD?

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?

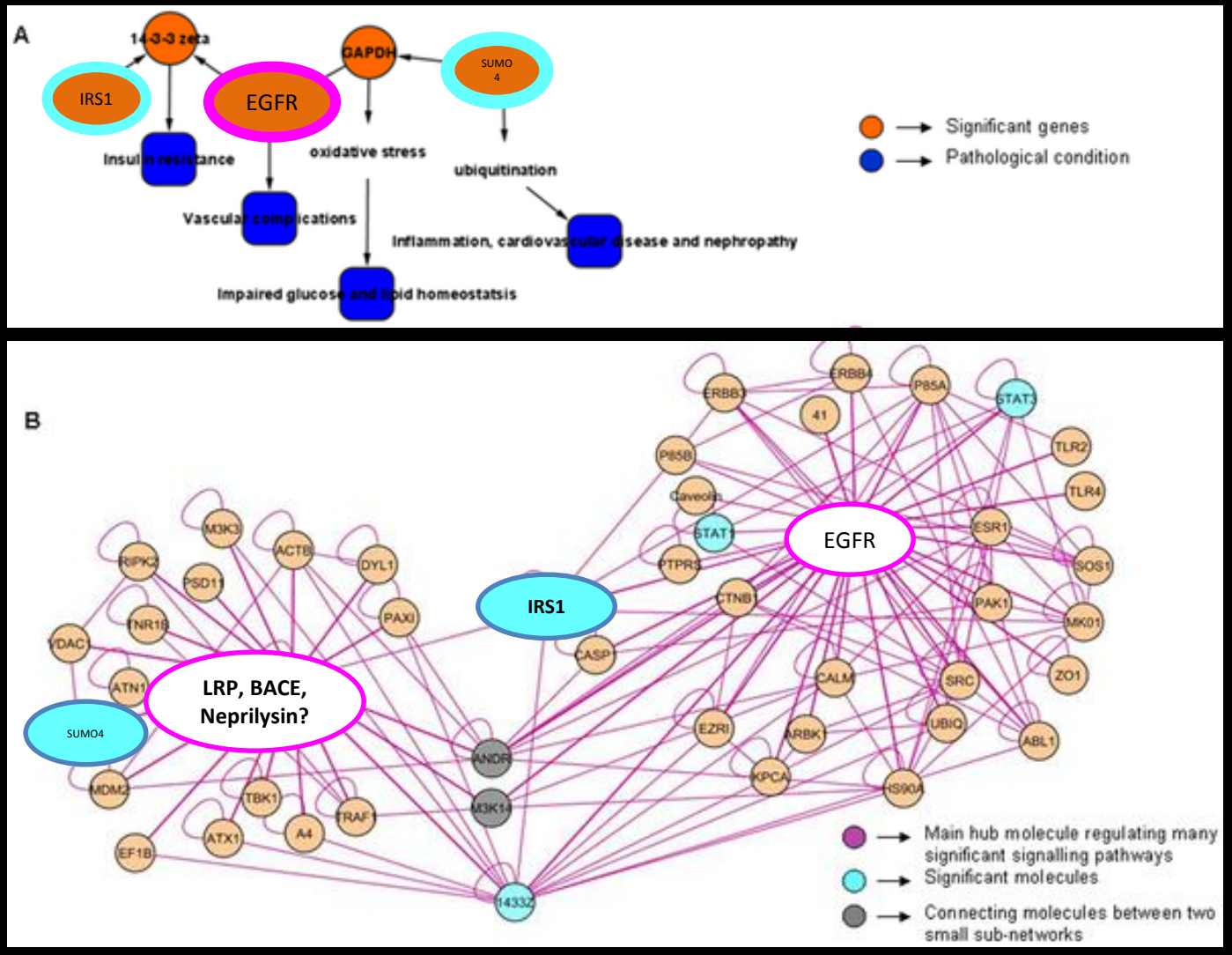
Systems Biology Approach to Complex Genetic-Environmental disease: (General theory with “Koch’s” Postulates = special theory)



Meng Q et al. Obesity, Diabetes, and Cardiovascular Disease. Curr Cardiovasc Risk Rep 2013: 7: 73-83.

Diabetic Microvascular-Complication Network

EGFR-Induced Insulin Resistance and Impaired GAPDH-Induced Microvascular Complications



Sengupta U et al. PloSONE 2009; 4: e8100.

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