Modifiable risk factors for cognitive decline,
MCI and AD in Northern Manhattan

José A. Luchsinger MD MPH
Columbia University Medical Center
New York, NY

Alzheimer's disease
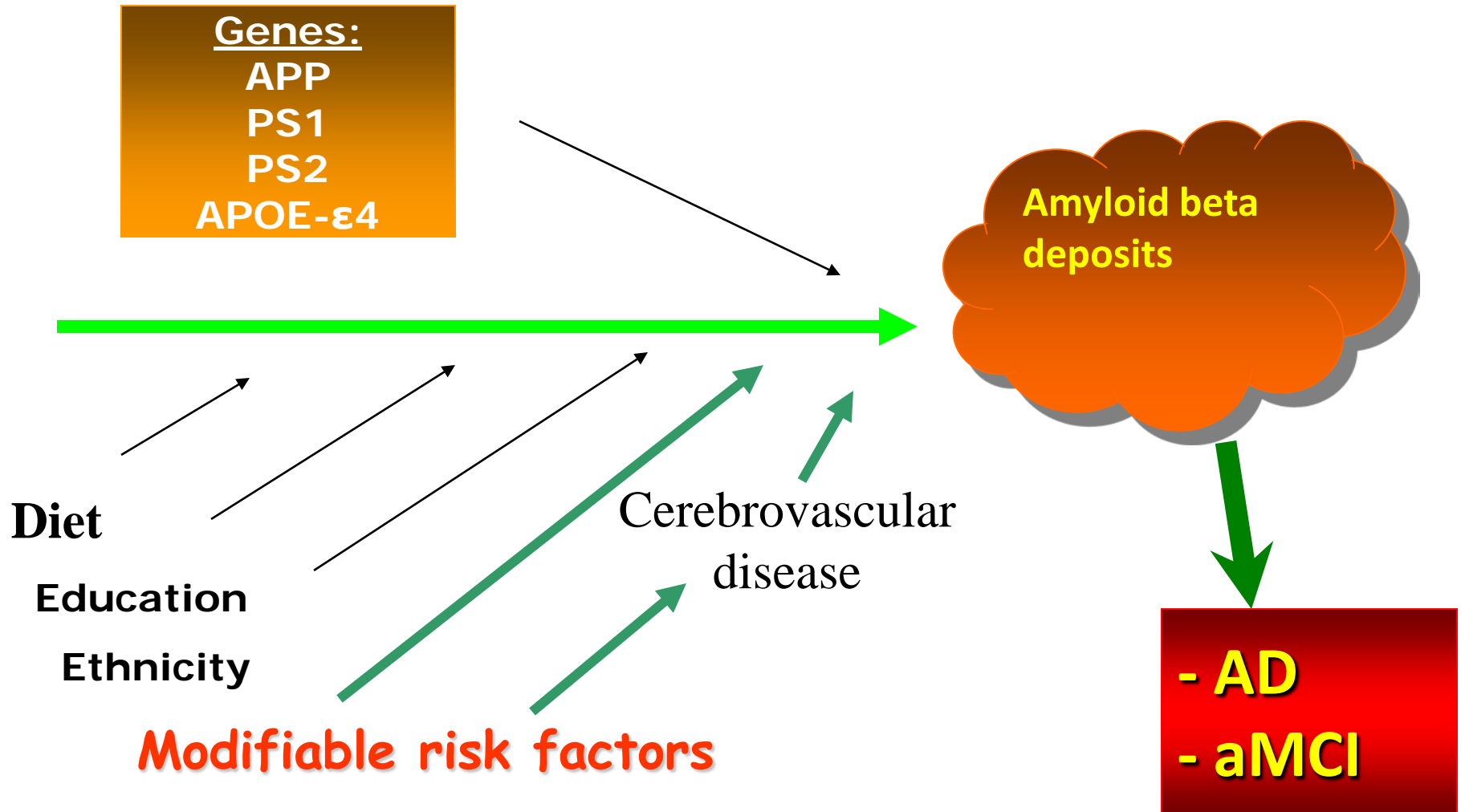
Vascular cognitive syndromes

Modifiable risk Factors:
Hypertension
Diabetes
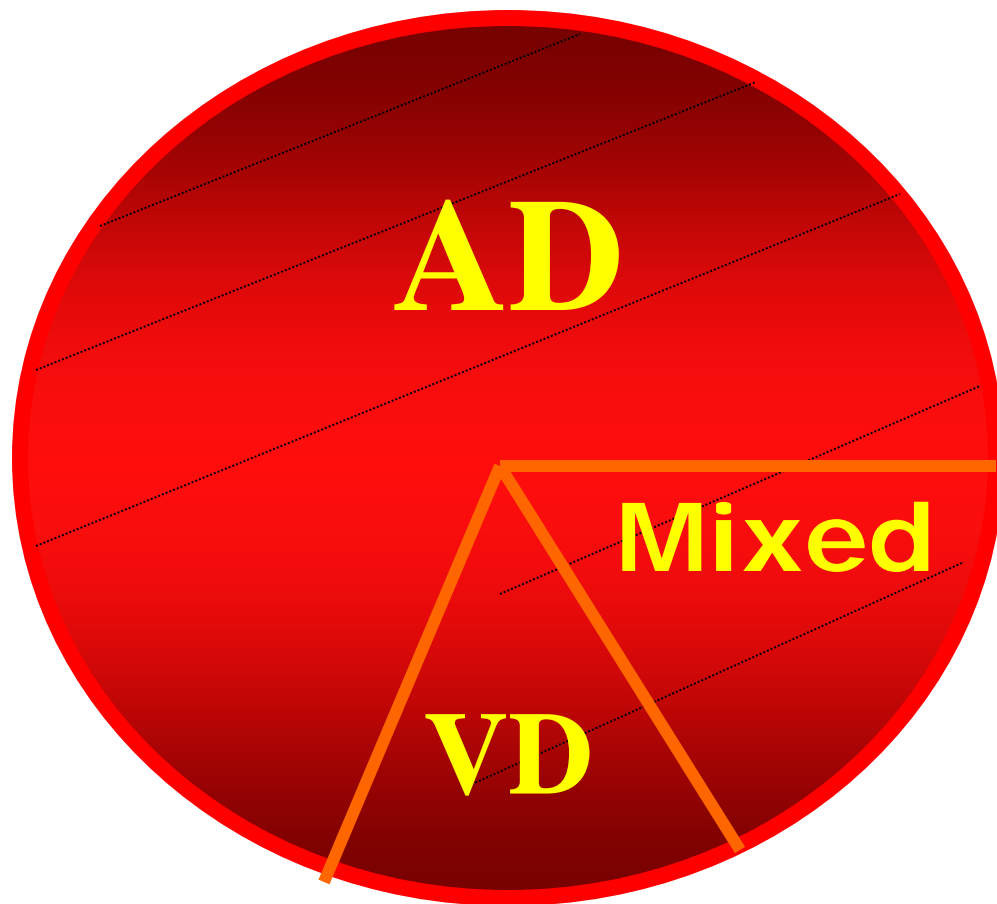Dyslipidemia
Smoking

→

Stroke
White matter disease

↓
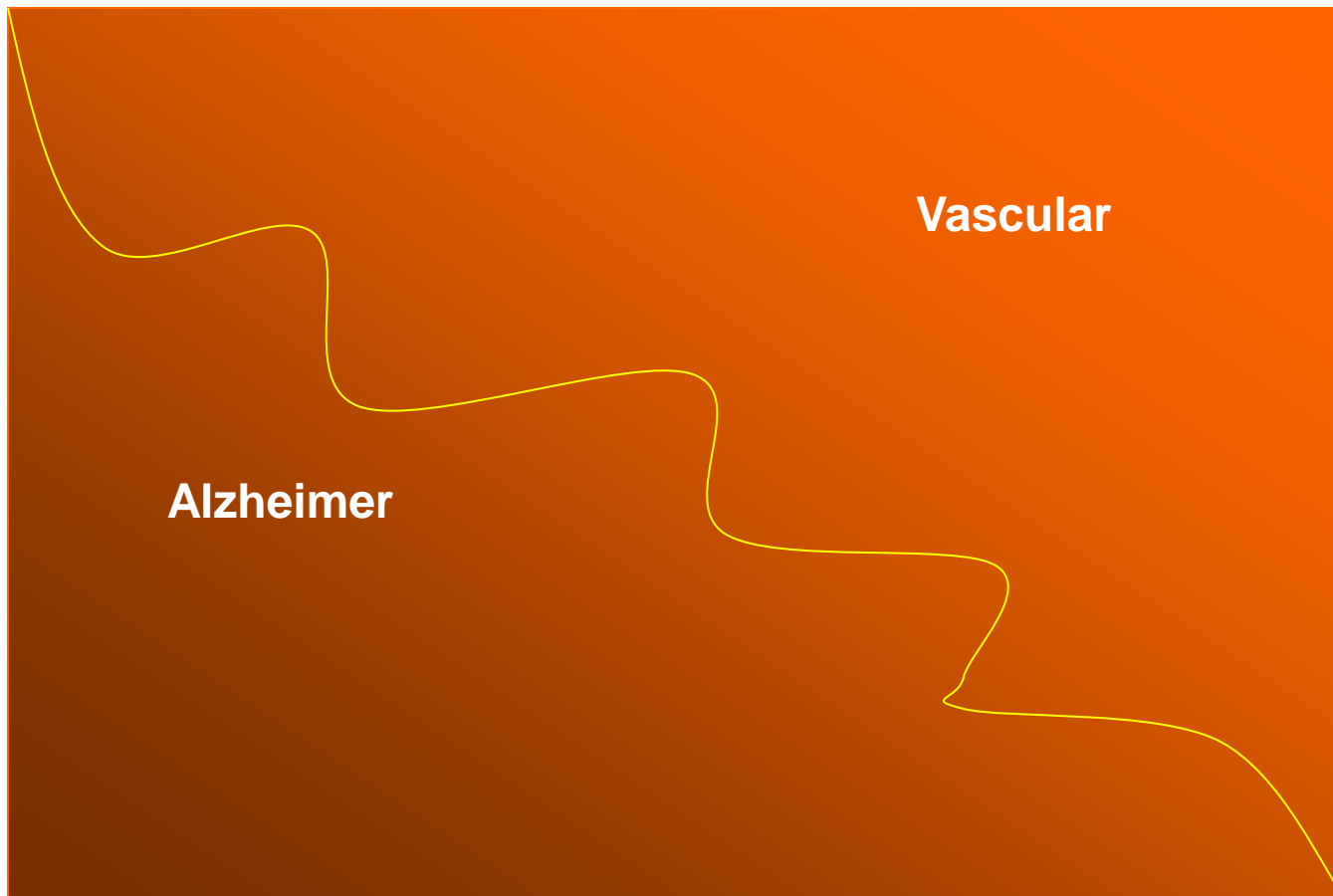
Vascular cognitive impairment
Vascular dementia
Non-amnestic MCI
Dysexecutive syndrome
????

Normal cognition   Mild cognitive impairment   Dementia
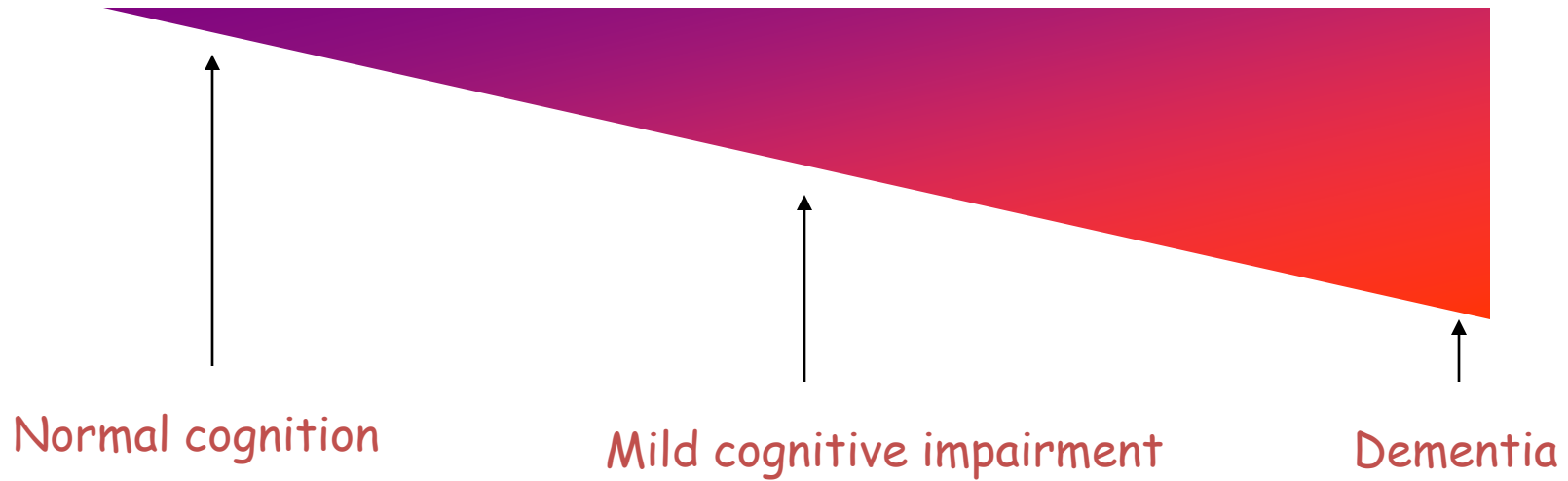
INWOOD

WASHINGTON HEIGHTS

HAMILTON HEIGHTS
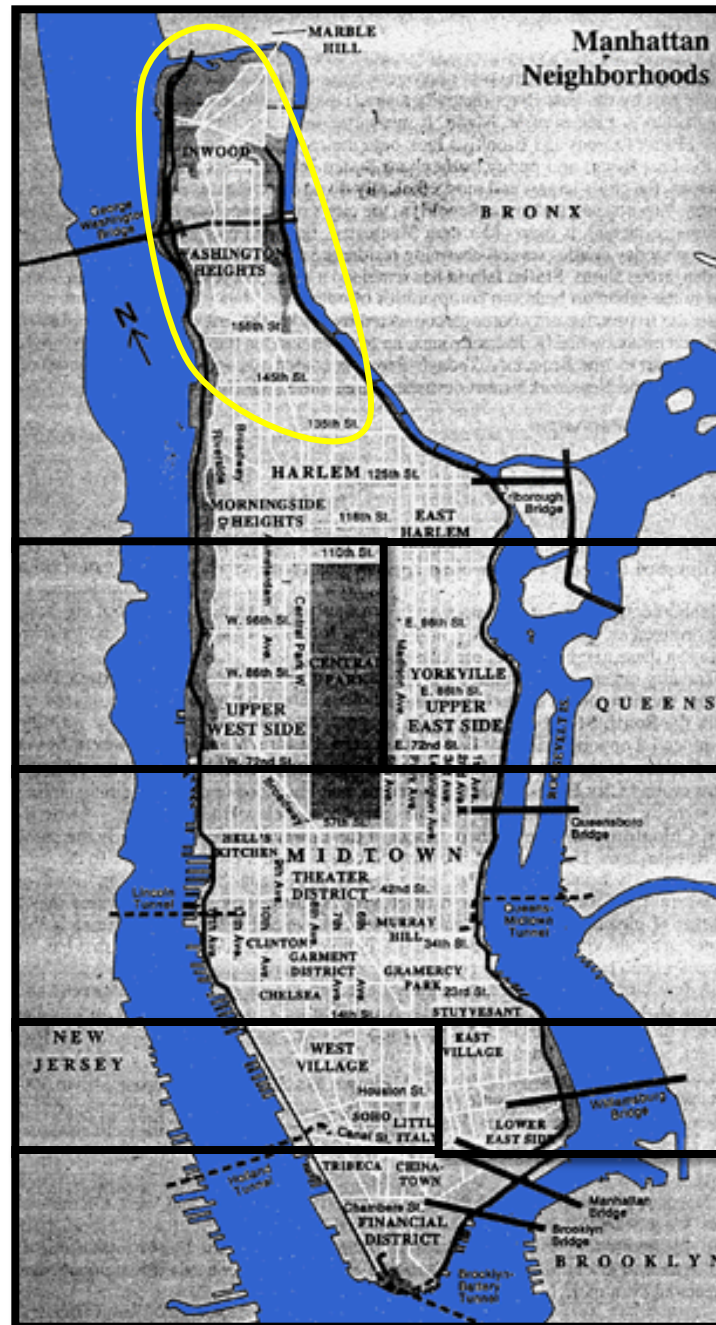
WHICAP (PI: R. Mayeux)

- Longitudinal study of aging in Northern Manhattan

- > 64 years

- Multiethnic
  - 44% Hispanic
  - 32% African American
  - 24% White

- Without dementia at baseline

- Mean follow-up > 6 years

Outcome measures

- Dementia
  - DSM IV
  - NINDS-AIREN
- MCI
  - Similar to Petersen's definition
  - Amnestic
  - Non Amnestic

- 4 cognitive scores from factor analysis
  - Memory
  - Executive
  - Visuospatial
  - Language

Questions pursued

- Is a risk factor associated with dementia or MCI?
  - Survival analyses
- Is a relation with dementia mediated by vascular mechanisms?
  - Attenuation of coefficients
- Does a risk factor modify cognitive decline?
  - Mixed models or GEE
- Could a risk factor modify the progression from MCI to dementia?
  - Logistic regression

Modifiable risk factors

- Diabetes:
  - Prevalence approximately 20%
  - ascertained by history

- Hypertension:
  - Prevalence approximately 70%
  - Ascertained by history or BP

Diabetes: relation to dementia

Alzheimer disease	**1.7** (**1.2,2.5**)
DAS	**2.8** (**1.5,5.2**)
All dementia	**1.9** (**1.4,2.6**)

Diabetes: relation to MCI

Table 3. HRs and 95% CIs Relating Diabetes to MCI, Amnestic MCI, and Nonamnestic MCI*

	MCI Cases (Rate)	Model 1		Model 2		Model 3	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause MCI							
No diabetes	241 (7.2)	1.0		1.0		1.0	
Diabetes	93 (9.4)	1.4 (1.1-1.8)	.007	1.3 (1.0-1.7)	.03	1.4 (1.0-1.8)	.04
Amnestic MCI							
No diabetes	117 (3.5)	1.0		1.0		1.0	
Diabetes	43 (4.4)	1.4 (1.0-1.9)	.05	1.5 (1.0-2.1)	.04	1.5 (1.0-2.2)	.02
Nonamnestic MCI							
No diabetes	124 (3.7)	1.0		1.0		1.0	
Diabetes	50 (5.1)	1.4 (1.0-1.9)	.04	1.3 (0.9-1.8)	.21	1.2 (0.9-1.8)	.22

Abbreviations: CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment.
*Model 1 is adjusted for age and sex; model 2 is also adjusted for ethnic group, years of education, and *APOE* ε4; and model 3 is also adjusted for hypertension, low-density lipoprotein cholesterol level, current smoking, heart disease, and stroke. Rates are per 100 person-years.

Luchsinger, J. A. et al. Arch Neurol 2007;64:570-575.

ARCHIVES OF
NEUROLOGY

Hypertension: relation to dementia

Hypertension	Total at risk	Developed AD, n (%)	AD, RR (95% CI)	Developed VaD, n (%)	VaD, RR (95% CI)
Present	731	84 (11.5)	0.9 (0.7–1.3)	39 (5.3)	1.8 (1.0–3.2)[*]
Absent	528	73 (13.8)	1.0 (reference)	17 (3.2)	1.0 (reference)

Unadjusted risk ratio (RR) and 95% CI are shown. When AD model was repeated adjusting for age, education, ethnic group, and history of heart disease, the RR decreased to 0.8 (95% CI, 0.6–1.1). Similarly, the RR decreased to 1.6 (0.9–2.9) for the VaD model when it was adjusted for these factors. The RR did not change when stratified by treatment.

* p = 0.05.

Posner, Neurology 2002

Hypertension: relation to MCI

Table 2. Data Relating Hypertension and the Risk of Incident MCI[a]

MCI Subtype	Incident MCI, No. (%)	Model[b]		
		1	2	3
All-cause MCI				
Group without hypertension	**76** (26.0)	1	1	1
Group with hypertension	**258** (41.2)	1.40 (1.06-1.77)[c]	1.30 (1.02-1.73)[c]	1.20 (0.81-1.69)
Amnestic MCI				
Group without hypertension	42 (14.4)	1	1	1
Group with hypertension	118 (18.8)	1.10 (0.79-1.63)	1.10 (0.80-1.67)	0.90 (0.54-1.47)
Nonamnestic MCI				
Group without hypertension	34 (11.6)	1	1	1
Group with hypertension	140 (22.4)	1.70 (1.13-2.42)[c]	1.60 (1.06-2.29)[c]	1.60 (0.93-2.85)

Abbreviation: MCI, mild cognitive impairment.

[a] A Cox proportional hazards model was used, with age at onset as the time variable, as described in the "Statistical Analyses" subsection of the "Methods" section.

[b] Data are given as hazards ratio (95% confidence interval). Model 1 was adjusted for sex and age; model 2, adjusted for age, sex, years of education, ethnic group, and *APOE* genotype; and model 3, adjusted for sex, age, ethnic group, years of education, *APOE* genotype, stroke, diabetes mellitus, heart disease, current smoking, and low-density lipoprotein cholesterol level. In all models, the group without hypertension was the reference group.

[c] Significant difference vs the group without hypertension.

Reitz, C. et al. Arch Neurol 2007;64:1734-1740.

ARCHIVES OF
NEUROLOGY

Progression from MCI to dementia

- Diabetes and Hypertension not related to progression from MCI to dementia

- Caveats:
  - Prevalent vs incident MCI
  - Short follow-up time
  - Temporal relationship between risk factor and MCI

Risk factors and cognitive decline

- Persons with diabetes had lower memory and executive scores at baseline and follow-up, but the slopes of decline were parallel (evidenced by a non-significant interaction term for time and diabetes from mixed models)

- Persons with hypertension had a similar pattern for decline in executive scores

Limitations

- Misclassification of dementia subtype
- Stability of MCI diagnosis
- Old age vs middle age
  - Lines of cognitive decline may have "split" before onset of follow-up
- Measurement of risk factors
  - Lack of proper measures of severity and duration
  - Bias towards the null

Conclusions

- Diabetes is related to both amnestic and non-amnestic forms of cognitive impairment

- Hypertension seems to be related mostly to non-amnestic forms of cognitive impairment

- **These associations are consistent with different but related outcomes in the natural history of cognitive decline**

Conclusions

- These associations appear to depend on insults that began before the time of observation

- Thus, studies in younger age groups are needed

- Specific NS domains could be used as early proxies for future cognitive impairment diagnoses

Acknowledgements

WHICAP (R01 AG037212)

Richard Mayeux, MD

Rafael Lantigua, MD

Nicole Schupf, PhD

Jennifer Manly, PhD

Ming X. Tang, PhD

Christiane Reitz, MD

Adam Brickman, PhD

Howards Andrews, PhD

**Scott Small, MD**

Domenico Accilli, MD (DERC)

Funding

– **National Institute on Aging**
– **New York City Council Speaker's fund for Public Health Research**
– **Fidelity foundation**
– **Alzheimer's Association**
– **Center for Medicare Services**
– **Institute for the Study of Aging**
– **Florence and Herbert Irving Clinical Research Scholars Program**
- **American Diabetes Association**

Take a deep breath!

http://www.encaletado.com/topocho/

Cognitive scores

- Memory : Selective Reminding Test and BVRT recognition);

- Language (15-item Boston Naming Test, BDAE repetition, and BDAE comprehension);

- Executive function (Mattis Identities and Oddities, raw score on Wechsler Adult Intelligence Scale–Revised Similarities subtest, and category and letter fluency);

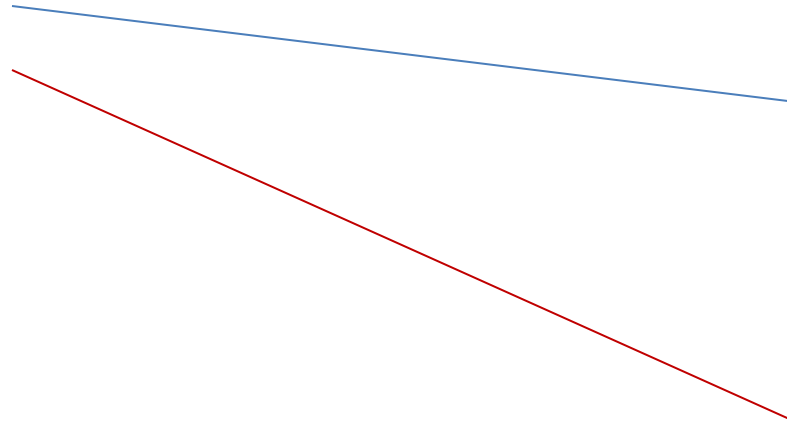- Visuospatial skill (Rosen Drawing Test and BVRT matching)

Risk factor in relation to cognitive decline
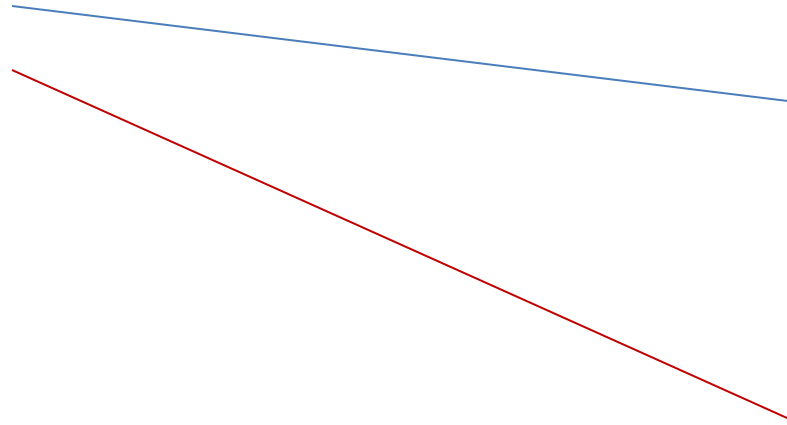
	Coefficient	P value
Risk factor		
Time		
interaction		

Risk factor in relation to cognitive decline

	Coefficient	P value
Risk factor		
Time		
interaction		