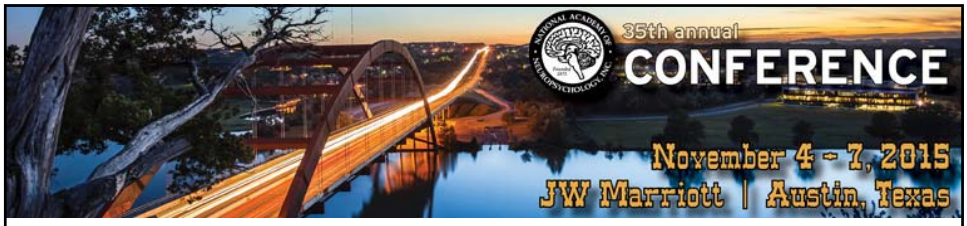

Translational Aging Research Considerations for Working with Mexican Americans: From Culture to Biology

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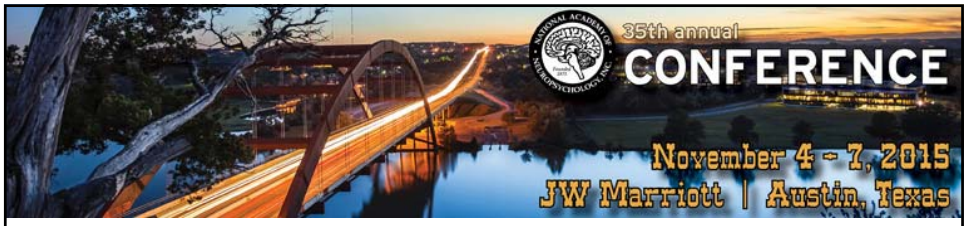


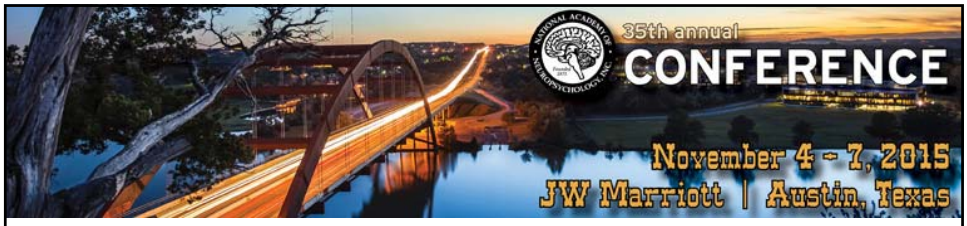
Financial Disclosure

I have financial relationships to disclose:

Research support from: Toyama Chemicals, NIH, EPA, NAN, CMS, Texas, multiple foundations

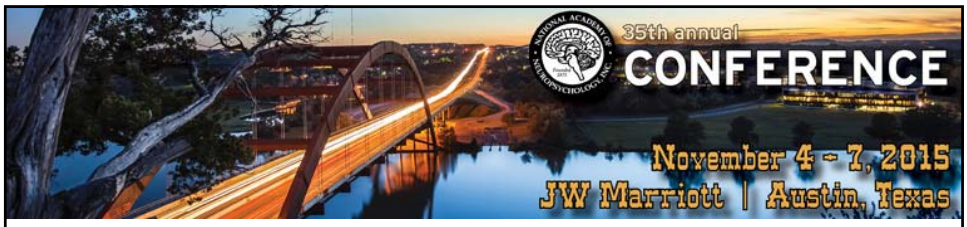
Multiple Commercial Methods Developed

- **Blood Test for Alzhiemer's Disease**
- **Blood-based screening tool for neurodegenerative disease**
- **Personalized medicine approach to treating cognitive loss**

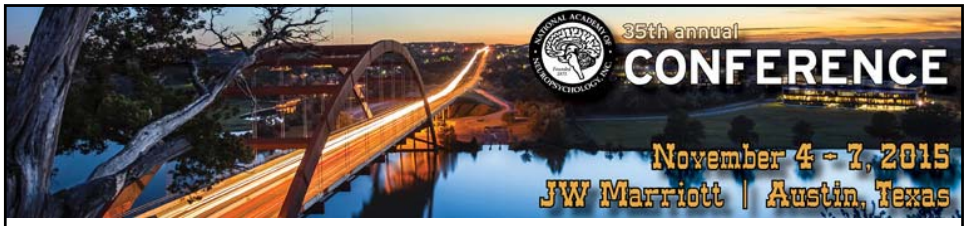


Objectives

- Discuss important factors for the conduct of clinical interviews among Mexican Americans
- Discuss normative considerations among Mexican American elders
- Discuss the differential expression of comorbidities among Mexican Americans that have an impact on neuropsychological functioning
- Discuss proteomic expression of Alzheimer's disease among Mexican Americans

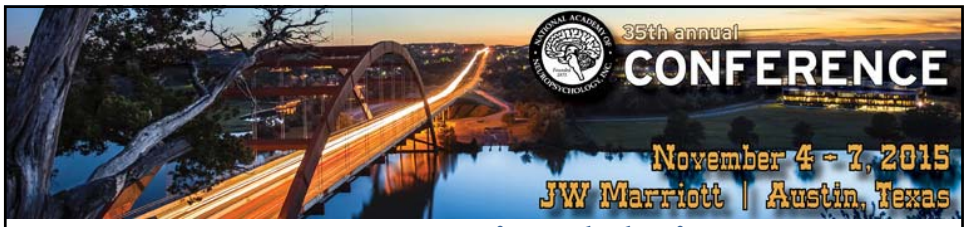


COGNITIVE AGING



Cognitive Aging

1. Elderly segment of the U.S. is growing at a rapid rate
2. 85+ are fastest-growing segment of the elderly pop
3. 40 million Americans age 65+; additional 14 million reaching 65 in the next 5 years



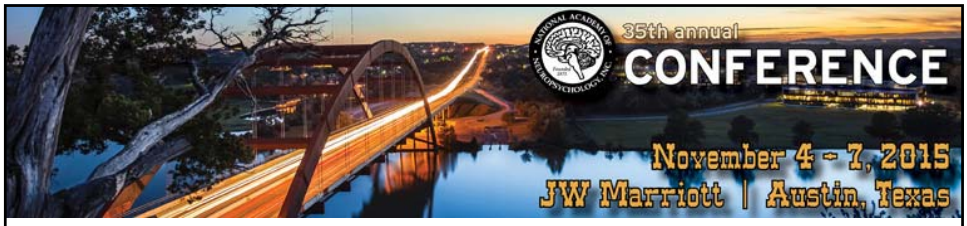
How Common is Alzheimer's Disease?

- 13% of those 65+
- Approximately ½ of those over 85

- Age 65-74 = 2%
- Age 75-84 = 19%
- Age 85+ = 42%

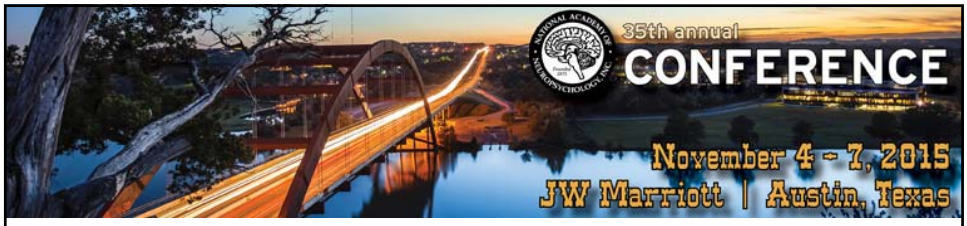
- Approximately 5.2 million Americans suffer from Alzheimer's disease; estimated that over 300,000 Texans suffer from AD

Alzheimer's Association



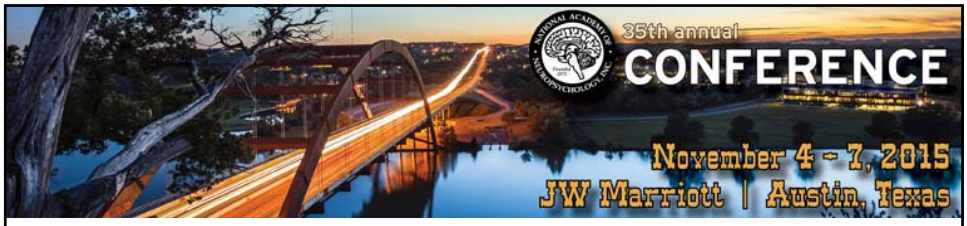
Symptoms of AD

- Difficulties learning and remembering information
  - Remote memory intact
- Misplacing things
- Repeating questions
- Disorientation in once familiar places
- Difficulty finding words
- Mood changes
  - Become withdrawn and isolated
- Do these changes:
  1. Reflect a change from prior levels?
  2. Impact daily activities?



How Common is Mild Cognitive Impairment?

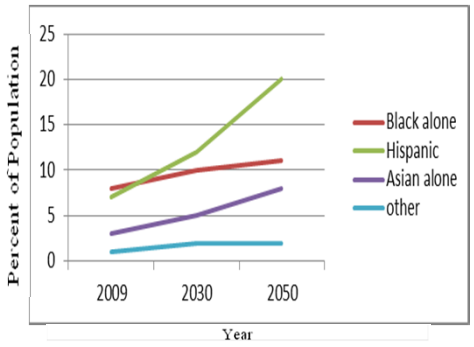
- MCI
  - "prodromal" category to AD or other dementias
  - Cognitive dysfunction/decline but maintain ADLs (they compensate)
  - Approx. 15% annual conversion rate from MCI to AD
  - Estimated 10-30% of those 65+ meet criteria for MCI
- Combined, 15-40% of adults 65+ meet criteria for MCI or AD

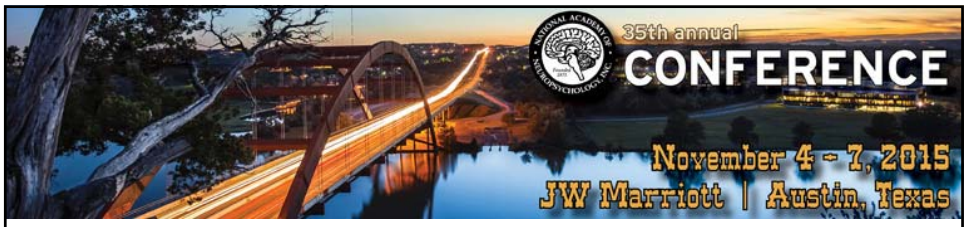


Growing Hispanic/Mexican American Elderly Population

1. Approximately 50% of the increase in the U.S. population from 2000-2010 was growth in the Hispanic community
2. The numbers of elders age 65+ will continue to grow over the next several decades
3. 65% of the U.S. Hispanic population is Mexican American

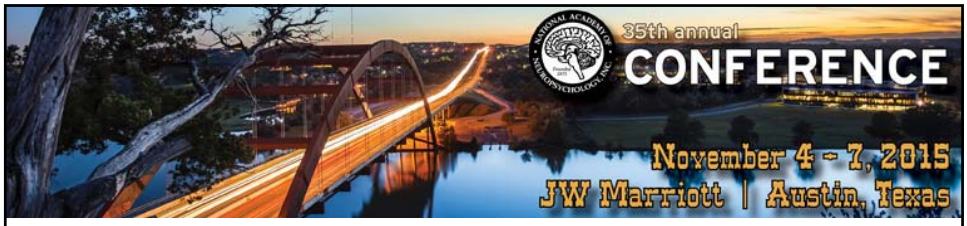
   The fastest aging segment of the U.S. population





Cognitive Aging/AD among Mexican Americans

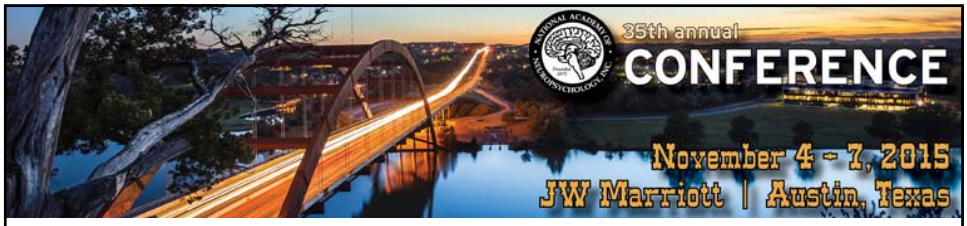
- It is anticipated that the rates of AD will grow six-fold among Hispanics by 2050
- Recent work has turned towards prevention efforts targeting the MCI state of cognitive dysfunction
- Recent work from our group suggests MCI/AD are different among Mexican Americans



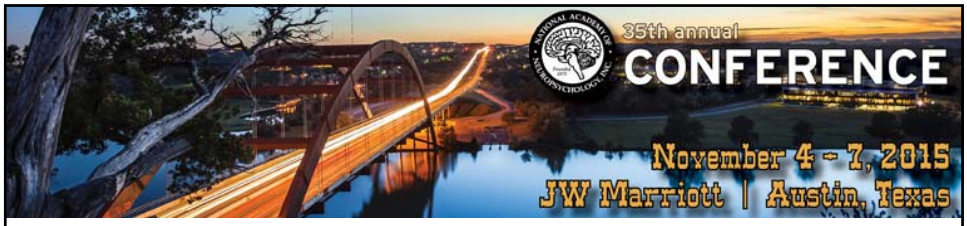
Health Disparities in MCI & AD among Mexican Americans

- May be at increased risk for AD & MCI
- Are diagnosed at younger ages and more advanced disease progression
- Are Less likely to receive formal dementia assessment or care
- Experience longer delays in assessments and receipt of treatments
- More likely to be cared for in home
- More likely to present with affective disturbances/distress (depression)
- Less likely to carry ε4 allele of APOE gene
- More likely to have multiple comorbidities including metabolic factors

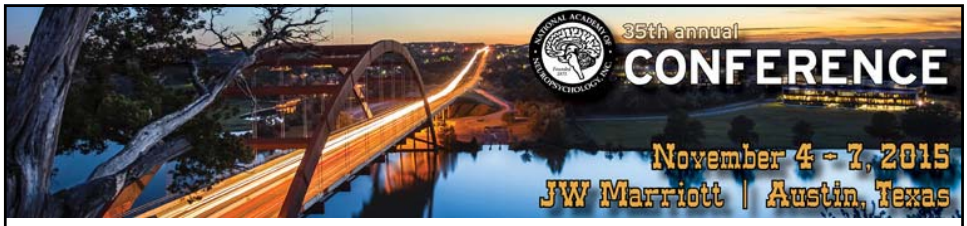
Alzheimer's Association, 2004; O'Bryant 2007; O'Bryant 2013; O'Bryant 2013; O'Bryant 2014



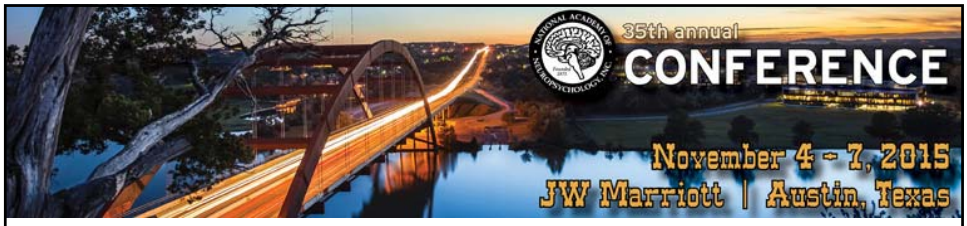
CONSIDERATIONS FOR CLINICAL INTERVIEWS WHEN WORKING WITH MEXICAN AMERICAN ELDERLY



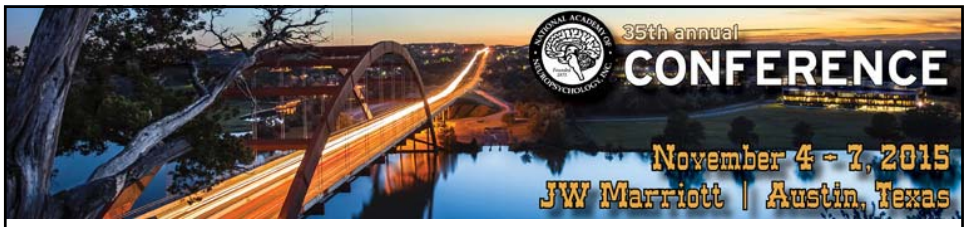
- DO NOT use term "Dementia"
- Patients and family members not likely to give you "the whole story" in 15min interview
- It is disrespectful for children to complain of parent's changes in cognitive abilities
- Informant report necessary for ADLs/IADLs review
  - Critical to MCI – AD differential diagnosis
- Family interpreters may give patients answers



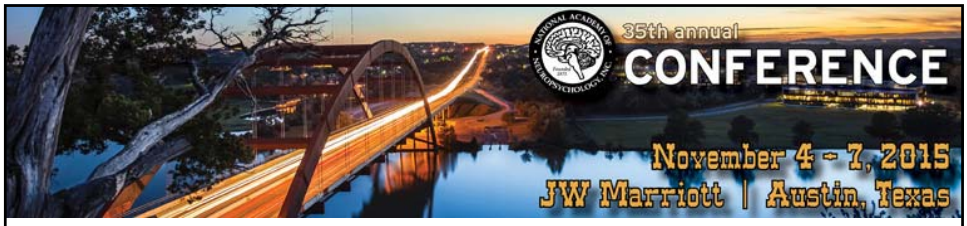
- Affective Complaints
  - More likely to complain of depression, anxiety and other affective distress
  - Many affective complaints will focus around physiological manifestations
  - Depression appears to be more strongly related to memory problems among Mexican Americans



NORMATIVE CONSIDERATIONS WHEN WORKING WITH MEXICAN AMERICAN ELDERLY

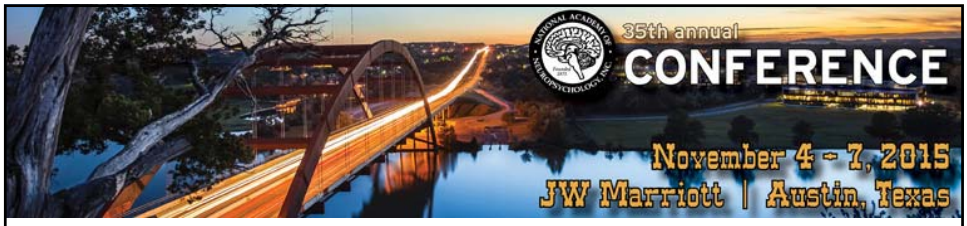


- How should normative references be adjusted?
  - Age? Education? Gender? Language? Other?



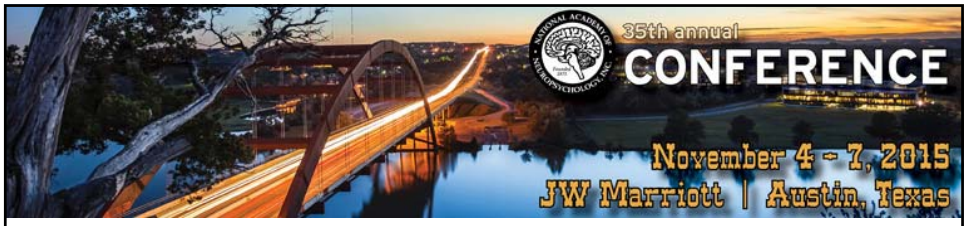
Texas Mexican American Normative Studies

- Leverages multiple cohorts:
  - Project FRONTIER
  - Texas Alzheimer's Research & Care Consortium
  - Health & Aging Brain among Latino Elders (HABLE)
- Combined data from cognitively normal adults and elders to create normative references
  - Normal – CDR = 0, MMSE normal, consensus review of normal cognition



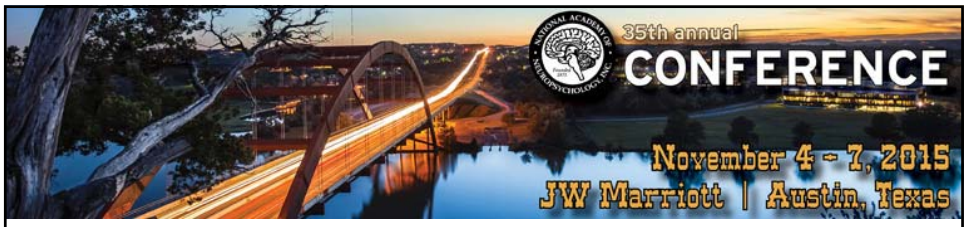
Tests and Sample Size

Test	Sample Size
MMSE	796
FAS	785
Animal Naming	781
BNT	533
CLOX1	771
CLOX2	771
Trails A	782
Trails B	714



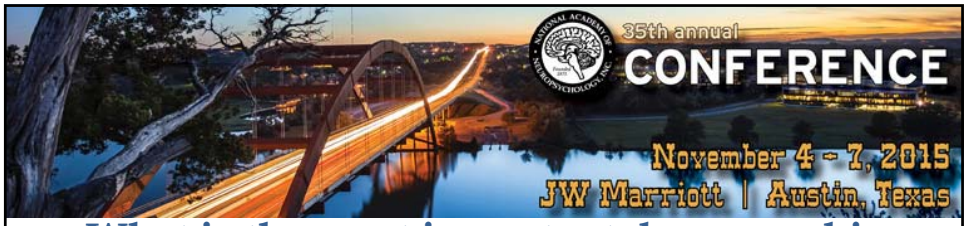
Tests and Sample Size

Test	Sample Size
EXIT	399
AMNART	449
WAT	274
CERAD LL	627
CERAD Recall	626
WMS3 LM1	642
WMS3 LM2	642
WMS3 Digits	645



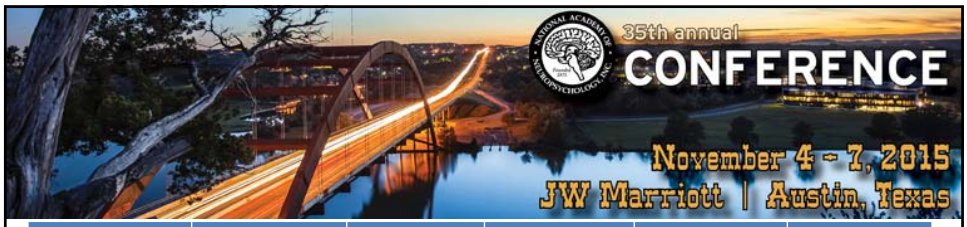
Tests and Sample Size

Test	Sample Size
WMS3 VR1	566
WMS3 VR2	544
RAVLT IR	266
RAVLT DR	266
RBANS	187

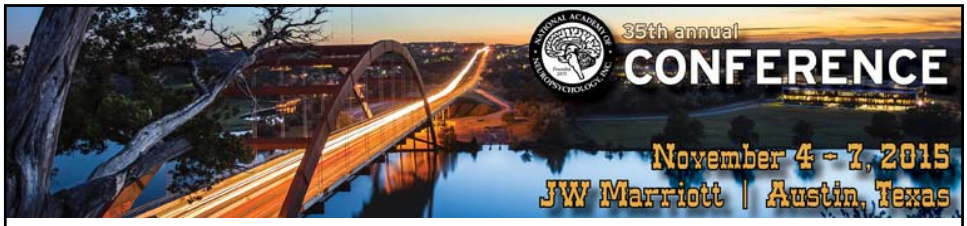


What is the most important demographic factor to consider?

Test		B(Std Error)	t-score	p-value	R^2
CLOX1	Education	.11(.02)	5.63	<0.001	.08
	Age	-.03(.01)	-2.77	=0.006	.02
CLOX2	Education	.13(.02)	7.93	<0.001	.14
Animals	Education	.31(.04)	7.66	<0.001	.12
	Age	-.08(.02)	-4.04	<0.001	.03
TMT A	Education	-2.21(.23)	-9.53	<0.001	.30
	Age	.55(.09)	6.01	<0.001	.05
	Test Language	9.45(2.67)	3.55	<0.001	.02
	Gender	-3.73(1.84)	-2.03	=0.04	.01
TMT B	Education	-7.67(.50)	-15.22	<0.001	.32
	Age	1.42(.22)	6.31	<0.001	.07
	Gender	11.24(4.64)	-2.43	=0.02	.01
FAS	Age	-.32(.05)	-6.81	<0.001	.11

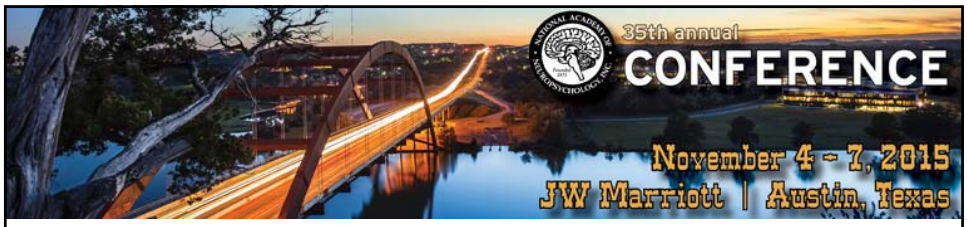


Test		B(Std Error)	t-score	p-value	R^2
CERAD LL	Education	.37(.06)	6.06	<0.001	.22
	Test Language	-3.93(.77)	-5.11	<0.001	.05
	Age	-.11(.03)	-3.82	<0.001	.03
	Gender	1.66(.45)	3.69	<0.001	.03
WAIS3 Digits	Education	.41(.04)	11.78	<0.001	.30
WMS3 LM1	Education	.79(.10)	7.59	<0.001	.14
	Gender	2.63(.99)	2.66	=0.008	.02
WMS3 LM2	Education	.50(.08)	6.46	<0.001	.11
	Gender	2.32(.74)	3.15	=0.002	.03
	Age	-.10(.05)	-2.28	=0.02	.01
CERAD LL Delay	Education	.12(.03)	4.43	<0.001	.15
	Age	-.06(.01)	-4.61	<0.001	.05
	Gender	.67(.20)	3.33	=0.001	.03
	Test Language	-.90(.34)	-2.61	=0.009	.02



Norms

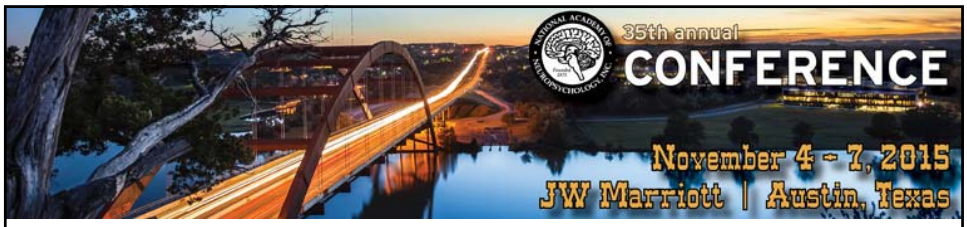
- Most norms utilize the "Mayo" methods –
  - Midpoint stratification by age ranges
- We utilized education as the primary stratification variable = education
  - Midpoint = 3, range = 0-6
  - Midpoint = 6, range = 3-9
  - Midpoint = 9, range = 6-12
  - >12
- Secondary stratification variable = age
  - <=60 and >60
- Multiple manuscripts in preparation to provide these norms to the community



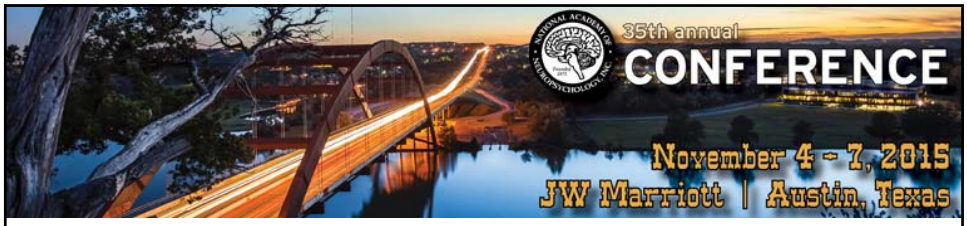
Other Considerations

- Is the normative reference appropriate for your patient?
- Where is the sample from?
- NEURONORMA Project – n=356 community-dwelling people age 49 and above

Scaled Scores: ages from 61+ and years of education from 0 to 6								
Scaled score	TMT-A	TMT-B	CLOX 1	CLOX 2	EXIT-25	FAS	Animal	Boston Naming
19								
18	≤26	≤73				≥45	≥24	54-60
17	27-29	74-84	14-15		0-1	38-44	23	52-53
16	30-32		13	15	2-3	37	21-22	51
15	33-37	85-98		14	4	34-36	19-20	48-50
14	38-41	99-115			5	31-33	17-18	47
13	42-46	116-143	12		6	28-30		45-46
12	47-54	144-154			7	24-27	15-16	40-44
11	55-59	155-180	11	13	8-9	21-23	14	37-39
10	60-65	181-201		12	10	17-20	13	34-36
9	66-77	202-233	10		11	15-16	11-12	29-33
8	78-98	234-254	9	11	12	12-14		27-28
7	99-109	255-299	8		13	10-11	9-10	22-26
6	110-128	>300			14-16	8-9	8	20-21
5	129-149		6-7	9-10	17-18	4-7	7	19
4	≥150		≤5	8	19			16-18
3				≤7	20	3	6	15
2					21	≤2	≤5	≤14
1					≥22			
Sample size (n)	104	73	106	107	64	101	104	91



MEDICAL COMORBIDITIES THAT CAN IMPACT COGNITION



Mexican American AD & MCI

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  - May be at increased risk for AD & MCI
  - Are diagnosed at younger ages and more advanced disease progression
  - Are Less likely to receive formal dementia assessment or care
  - Experience longer delays in assessments and receipt of treatments
  - More likely to be cared for in home
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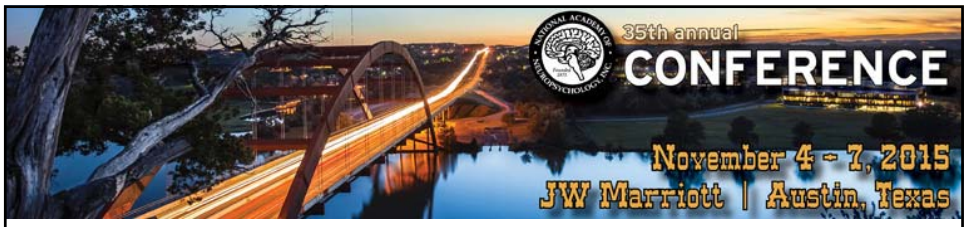
Alzheimer's Association, 2004; O'Bryant 2007; O'Bryant 2013a; O'Bryant 2013b; O'Bryant in press



Journal of Alzheimer's Disease 33 (2013) 373–379
DOI 10.3233/JAD-2012-121420
IOS Press

Characterization of Mexican Americans with Mild Cognitive Impairment and Alzheimer's Disease

Sid E. O'Bryant[a,b,*], Leigh Johnson[a,b], Valerie Balldin[c], Melissa Edwards[a,d], Robert Barber[b,e], Benjamin Williams[f], Michael Devous[g], Blair Cushings[h], Janice Knebl[a] and James Hall[b,i]

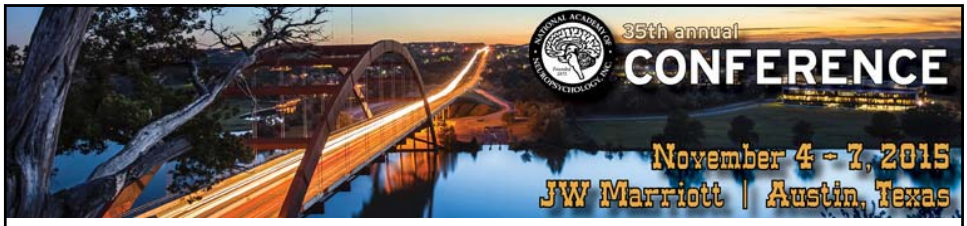
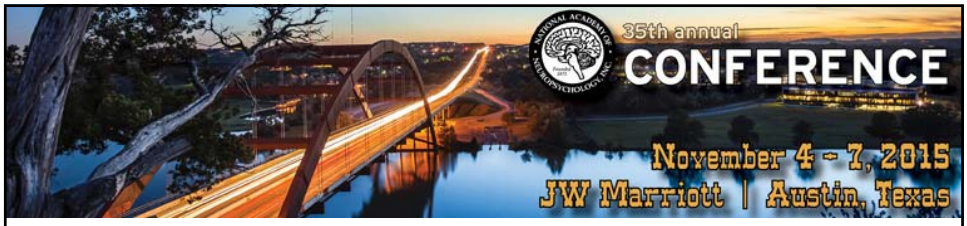


Table 1
Demographic characteristics

	Mexican American			Non-Hispanic White		
	AD ($n=35$)	MCI ($n=67$)	NC ($n=337$)	AD ($n=160$)	MCI ($n=97$)	NC ($n=376$)
Age (years)	73.6 (9.1)	61.9 (12.3)	58.7 (9.9)	79.4 (7.0)	74.4 (10.6)	65.6 (11.5)
Education (years)	5.9 (4.5)	6.6 (4.2)	8.1 (4.2)	13.2 (3.2)	12.4 (2.5)	14.3 (2.8)
Gender (%male)	45%	38%	29%	39%	33%	32%
MMSE	18.5 (5.0)	24.7 (3.6)	27.5 (2.8)	21.6 (4.6)	26.1 (2.7)	29.0 (1.3)
CDR SB	5.5 (3.6)	0.8 (1.0)	0.1 (0.4)	5.4 (3.3)	1.2 (1.1)	0.1 (0.4)
GDS	9.8 (5.5)	9.3 (1.5)	6.1 (5.6)	5.9 (4.4)	5.6 (0.7)	4.4 (4.7)
Depressed (%yes)	46%	44%	21%	18%	29%	10%
ApoEε4 positive	38%	26%	19%	60%	37%	23%
Diabetes	46%	51%	35%	14%	29%	16%
Obese	27%	45%	47%	13%	16%	25%

AD, Alzheimer's disease; CDR SB, Clinical Dementia Rating Scale sum of boxes score; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; NC, normal control.



ELSEVIER

Alzheimer's & Dementia 9 (2013) 622–631

Alzheimer's & Dementia

Featured Article

Risk factors for mild cognitive impairment among Mexican Americans

Sid E. O'Bryant[a,b,*], Leigh Johnson[a,b], Joan Reisch[c], Melissa Edwards[d], James Hall[b,e], Robert Barber[b,f], Michael D. Devous, Sr.,[g], Donald Royall[h,i], Meharvan Singh[b,f]

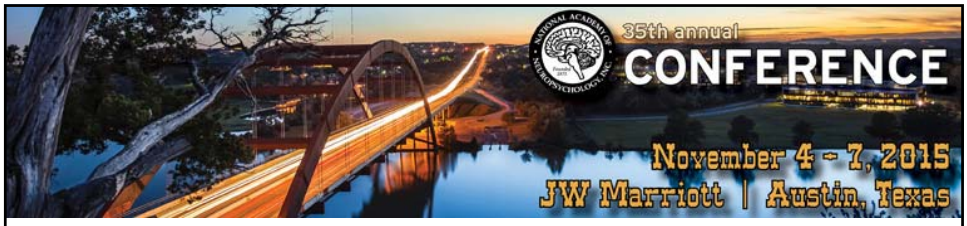
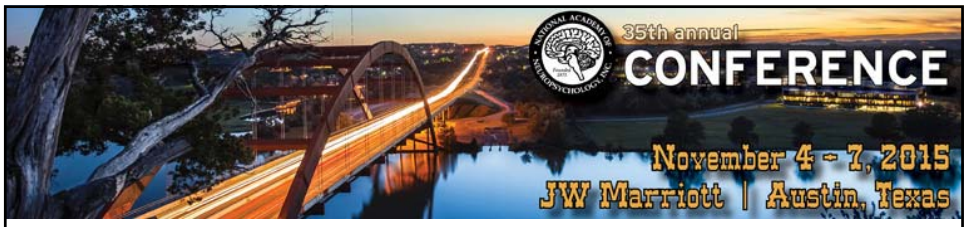


Table 4
OR for potential MCI risk factors by cohort

	TARCC		FRONTIER	
	OR (95% CI)		OR (95% CI)	
	Mexican American	Non-Hispanic	Mexican American	Non-Hispanic
Age	1.16 (1.10–1.22); $P < .001$	1.04 (1.02–1.07); $P = .002$	1.08 (1.03–1.14); $P = .002$	1.06 (1.03–1.09); $P = .001$
Gender	0.56 (0.28–1.11); $P = .10$	0.56 (0.35–.090); $P = .017$	0.53 (0.23–1.23); $P = .15$	2.55 (1.09–6.07); $P = .03$
Education	1.01 (0.88–1.16); $P = .87$	0.87 (0.79–0.95); $P = .003$	1.04 (0.93–1.18); $P = .49$	0.74 (0.62–0.88); $P < .001$
Hypertension	1.68 (0.77–3.68); $P = .19$	0.67 (0.40–1.12); $P = .14$	1.37 (0.57–3.27); $P = .49$	1.79 (0.79–4.06); $P = .17$
Hyperlipidemia	1.05 (0.67–1.67); $P = .82$	1.23 (0.87–1.71); $P = .26$	1.10 (0.47–2.55); $P = .83$	0.40 (0.19–0.83); $P = .02$
Diabetes	1.70 (0.83–3.48); $P = .15$	0.92 (0.45–1.85); $P = .80$	1.84 (0.81–4.19); $P = .14$	2.53 (1.05–6.01); $P = .04$
Obesity	0.91 (0.45–1.85); $P = .79$	1.07 (0.82–1.40); $P = .63$	0.98 (0.43–2.22); $P = .96$	0.47 (0.19–1.13); $P = .10$
GDS score	1.22 (1.13–1.31); $P < .001$	1.17 (1.11–1.24); $P < .001$	1.05 (0.97–1.13); $P = .25$	1.05 (0.97–1.14); $P = .19$
APOE ε4	1.89 (0.83–4.34); $P = .13$	1.43 (0.88–2.30); $P = .15$	1.53 (0.60–3.90); $P = .38$	2.58 (1.05–6.07); $P = .02$

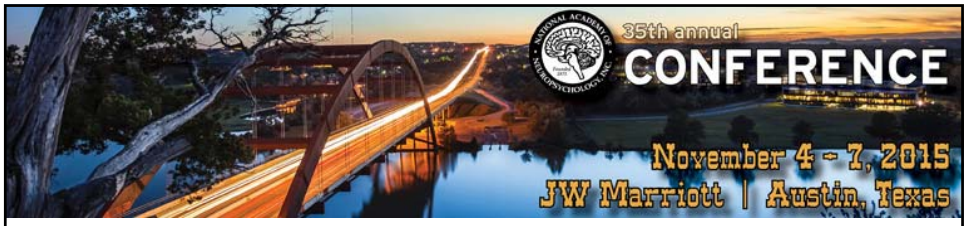
Abbreviations: *APOE*, apolipoprotein E; FRONTIER, Facing Rural Obstacles to health Now Through Intervention, Education & Research; TARCC, Texas Alzheimer's Research & Care Consortium.



Metabolic Factors and MCI/AD

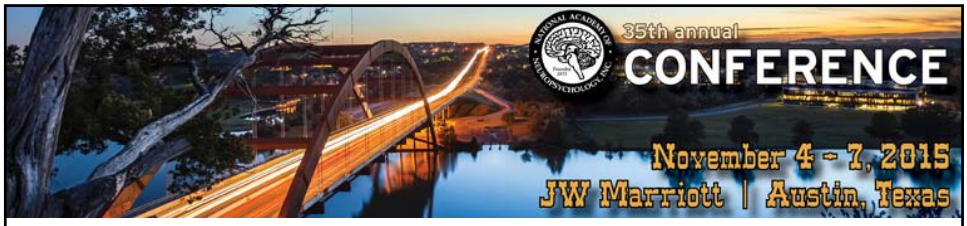
- In midlife, being overweight (BMI = 25-29) or obesity (BMI $\geq$ 30) conveys an increased risk for the development of AD
- However, in late life the pre-clinical phase of AD is associated with decreasing BMI (5-6 years before diagnosis)
  - A loss of 1.0 unit of BMI/year was associated with about a 25% increased risk of AD compared with persons experiencing no change in BM.
  - Individuals who progress to AD begin to lose about twice as much weight 1 year before symptom onset when compared to healthy controls.

Buchman et al. 2005; Gustafson et al. 2003; Johnson et al. 2006; Kivipelto et al. 2005; Rosengren et al. 2005; Whitmer et al. 2005; Yamada et al. 2003



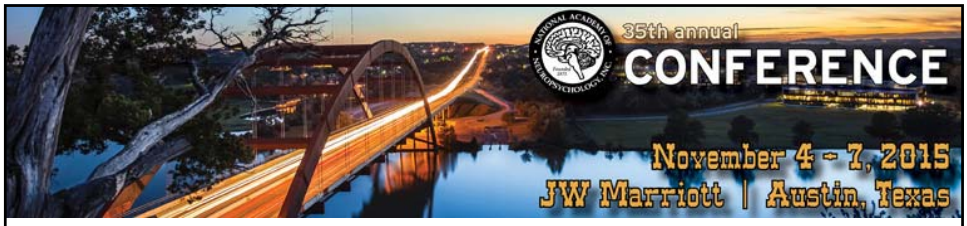
- Obesity is associated with other risk factors discussed including hypertension, hyperlipidemia, as well as diabetes and insulin resistance
- Obesity is related to chronic inflammation
- Adipose tissue produces a number of pro-inflammatory cytokines including TNFα, TGF-β, IL-1, IL-6 as well as CRP, an acute-phase reactant

Cancello & Clement, 2006; Tilg & Moschen, 2006



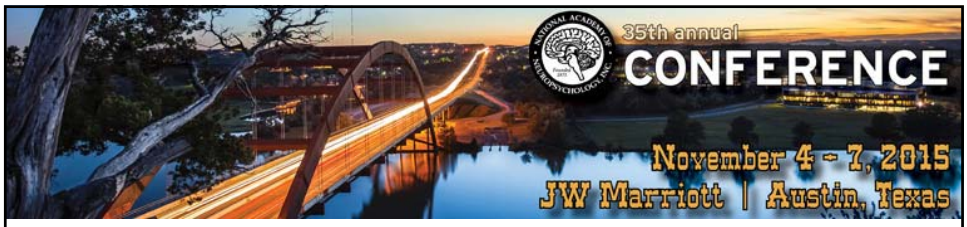
- Diabetes (particularly type-2) and insulin resistance have been found to convey a significantly increased risk for cognitive dysfunction, MCI & AD.
- **Honolulu-Asia Aging Study**
  - Those with diabetes and APO 4ε had significantly increased risk for AD as compared to those without APO 4ε (RR=5.5).
  - Those with both diabetes & APO 4ε allele had higher number of hippocampal plaques, hippocampal and cortical NFTs, as well as higher risk for cerebral amyloid angiopathy.
- **Rotterdam Study**
  - Those with diabetes had twofold increased risk for AD.
  - Those diabetes patients treated with insulin had greatest risk.
- **WHICAP project**
  - Diabetes and smoking were the strongest risk factors for incident AD
- **Sacramento Area Latino Study on Aging (SALSA study)**
  - Diabetes is associated with 10-year risk for dementia among Mexican Americans
- Results have not always been consistent

Arvanitakis et al. 2004; Kuusisto et al. 1997; Leibson et al. 1997; Luchsinger et al. 2005; Ott et al. 1999; Mayeda 2013; Peila et al. 2002; Razay & Wilcock, 1994; Xu et al. 2004



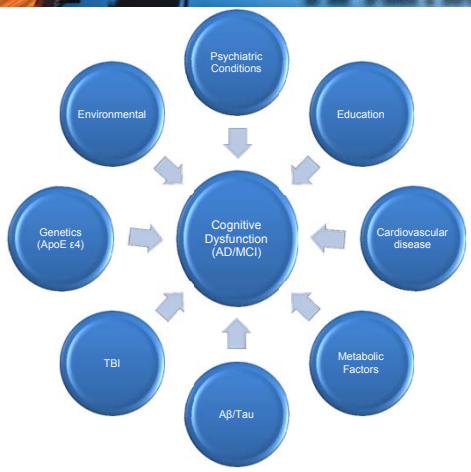
- Cortical atrophy is more pronounced in AD patients with DM and APO 4ε allele.
- Hyperglycemia has been linked to toxic microvascular changes.
- Detrimental effects of the metabolic syndrome (insulin resistance, hypertension, dyslipidemia, obesity, in addition to pro-thrombotic and pro-inflammatory states).
- Insulin has been linked to increased tau phosphorylation as well as increased metabolism (and decreased clearance through IDE) of Aβ.

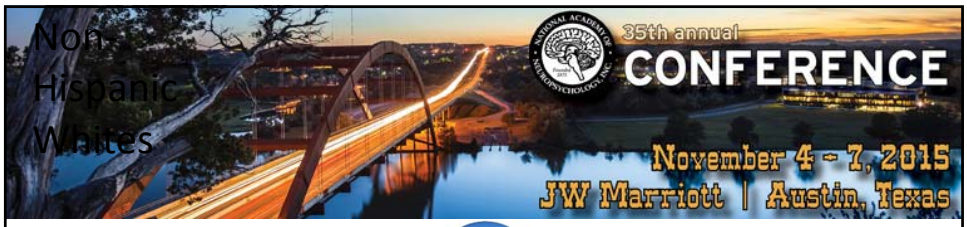
Biessels & Kappelle, 2005; Biessels et al. 2006; Freude et al. 2005; Gasparini et al. 2002; Nicolls 2004



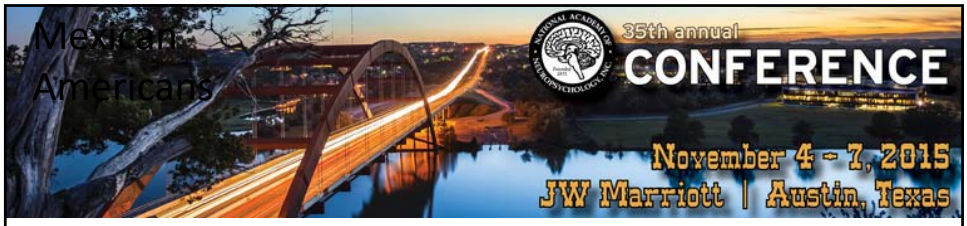
Why would MCI/AD vary by ethnicity?

Risk Factors



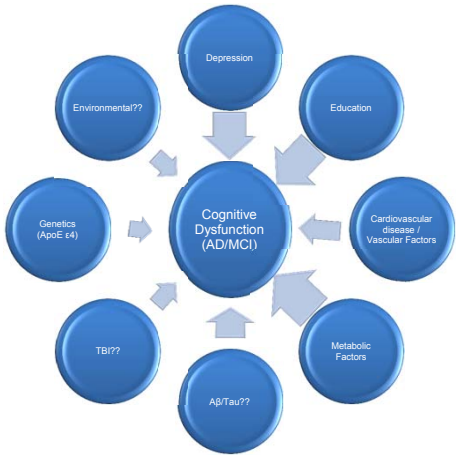


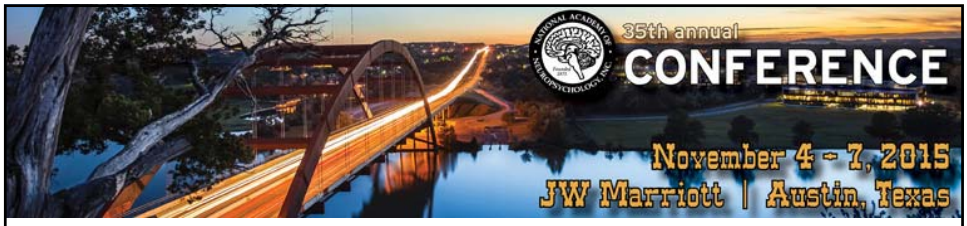
Non-Hispanic Whites



Mexican Americans

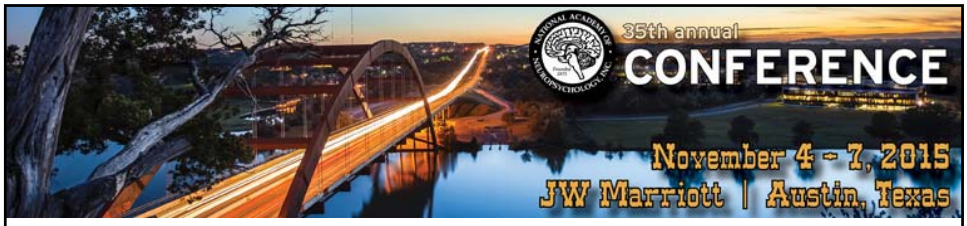
Mexican Americans





Metabolic Factors & MCI/AD Among Mexican Americans

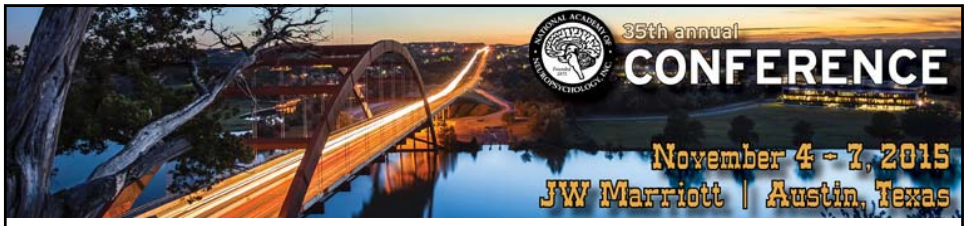
- Metabolic/CVD risk score (obesity + hypertension + dyslipidemia + diabetes):
  - Mexican Americans
    - FRONTIER (OR=1.33)
    - TARCC (OR=1.77)
  - non-Hispanic Whites
    - FRONTIER (0.98)
    - TARCC (OR=1.03)
- Currently examining the risk score in multiple other ways



Study examining the Hachinski Ischemic Index Scale

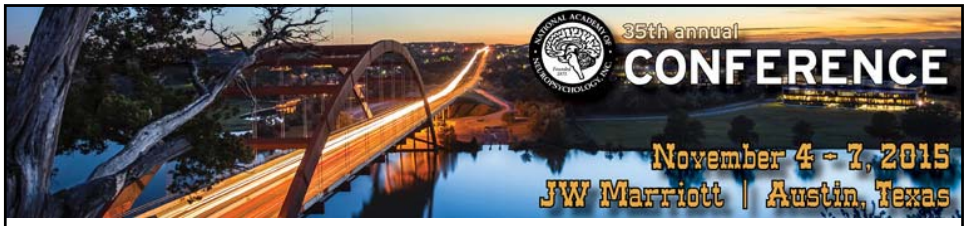
	Mexican American	Non-Hispanic Whites
	N=211	N=306
Age	55.5 (9.9)	65.4(12.6)
Education	7.5(4.1)	13.3(2.7)
Male	62	94
Female	149	212
MMSE	26.7(3.0)	28.4(1.9)
Hachinski	1.9(2.0)	1.9(2.0)
MCI diagnosis	32	42

Johnson et al 2014



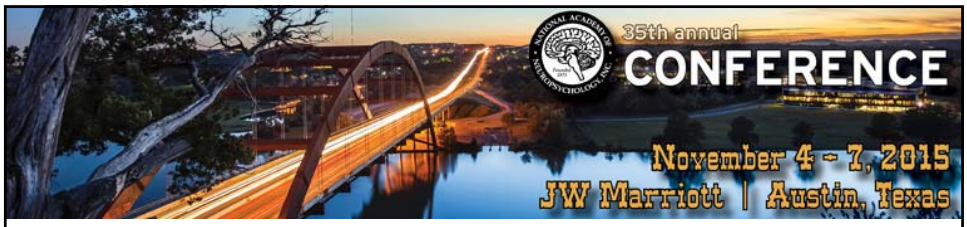
Study examining the Hachinski Ischemic Index Scale

	Mexican American		Non Hispanic White	
	B (SE)	P	B (SE)	P
MMSE	1.16(.09)	.09	-.13(.06)	.02*
Immediate Memory	-.78(.28)	.01*	-.85(.26)	.00*
Attention	-.74(.36)	.04*	-1.6(.36)	.00*
Delayed Memory	.37(.29)	.19	.14(.28)	.62
Language	-.24(.16)	.13	-.31(.16)	.05
Visuospatial	.02(.21)	.94	-.33(.18)	.07
Exit 25	.37(.14)	.01*	.46(.12)	.00*
MCI dx	OR=1.1	0.2	OR=1.3	0.01



Comorbidity of DM and Depression

- TARCC (clinic based, screened out for depression)
  - Mexican American = 8%
    - OR for MCI = 1.73 (p<0.005)
  - Non-Hispanic = 2%
    - OR for MCI = 0.98
- FRONTIER (community-based)
  - Mexican American = 20%
    - OR for MCI = 2.6
  - Non-Hispanic = 5%
    - OR for MCI = 2.9
- HABLE
  - Mexican American = 17%
  - Non-Hispanic = 10%



RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

The differential impact of depressive symptom clusters on cognition in a rural multi-ethnic cohort: a Project FRONTIER study

Sid E. O'Bryant[1,2], James R. Hall[3,4], Kelly C. Cukrowicz[5], Melissa Edwards[2], Leigh A. Johnson[6,7], David Lefforge[1], Marjorie Jenkins[6,8] and Andrew Dentino[7,9,10]

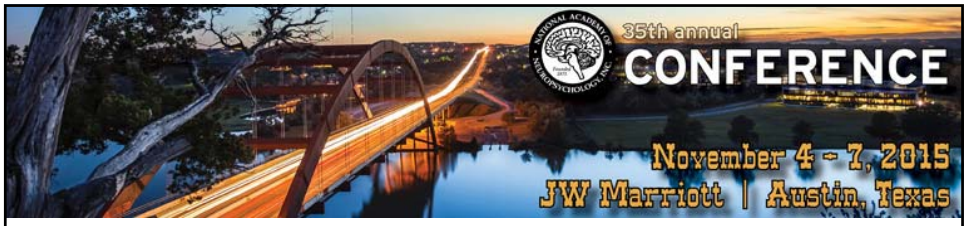
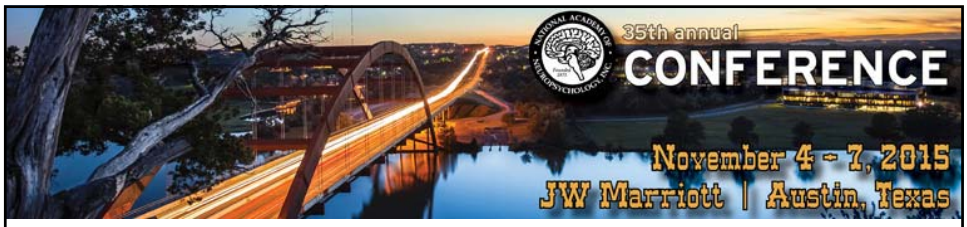


Table 4 Relation between GDS scores and RBANS index raw scores by ethnicity

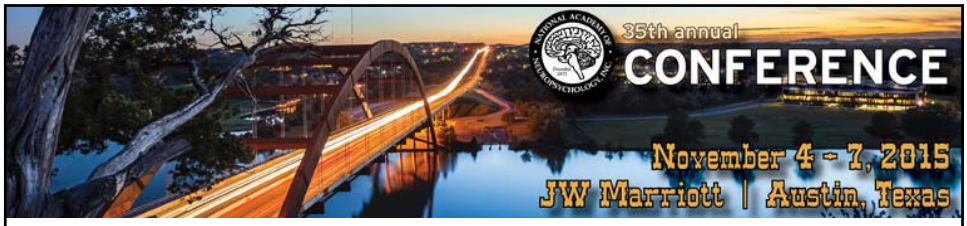
	RBANS immediate memory		RBANS visuospatial		RBANS language		RBANS attention		RBANS delayed memory	
	B	**p*-value	*B*	**p*-value	*B*	**p*-value	*B*	**p*-value	*B*	**p*-value
Hispanic										
GDS-30 dysphoria	−1.36	<0.001 15%	−0.54	0.003 9%	−0.67	0.006 6%	−0.44	0.24	−0.68	0.13
GDS-30 meaninglessness	−2.38	0.001 11%	−0.59	0.21	−0.80	0.02	−2.27	0.003 4%	−2.27	0.001 12%
GDS-30 apathy	0.18	0.79	−0.78	0.04	−0.23	0.50	−0.54	0.49	−0.39	0.57
GDS-30 cognitive impairment	−2.53	<0.001 16%	−0.66	0.05	−0.73	0.01	−1.66	0.01	−2.19	<0.001 15%
GDS-30 total score	−0.67	<0.001 16%	−0.28	0.002 10%	−0.18	0.02	−0.39	0.03	−0.57	<0.001 13%
Non-Hispanic										
GDS-30 dysphoria	−1.05	0.02	−0.57	0.08	−0.30	0.06	−1.38	0.02	−1.08	0.001 12%
GDS-30 meaninglessness	−1.57	0.03	−0.92	0.02	−0.90	0.02	−1.55	0.10	−1.77	0.02
GDS-30 apathy	−0.77	0.30	0.15	0.73	−0.10	0.79	−0.20	0.82	−1.02	0.13
GDS-30 cognitive impairment	−1.38	0.08	−0.87	0.08	−0.97	0.02	−2.41	0.02	−1.96	0.01
GDS-30 total score	−0.38	0.05	−0.18	0.16	−0.26	0.02	−0.53	0.03	−0.46	0.02

Note: Covariates entered into model = age, gender, education, and language of administration.
*Per cent variance accounted for by GDS-30 factor score provided where significant.



Chronic Kidney Disease

- ESRD is 1.5x higher among Hispanics
- Faster progression from CKD to ESRD
- Little literature on mild CKD and cognition among Hispanics
- HABLE
  - N=437 Mexican Americans analyzed
  - Grouping = eGFR <45, 45-59, and 60 or greater



CLINICAL INVESTIGATIONS

Association Between Cognitive Impairment and Chronic Kidney Disease in Mexican Americans

Harold M. Szerlip, MD,† Melissa L. Edwards, MA,*‡ Benjamin J. Williams, MD, PHD,§ Leigh A. Johnson, PhD,*‖ Raul M. Vintimilla, MPH,* and Sid E. O'Bryant, PhD*‖*

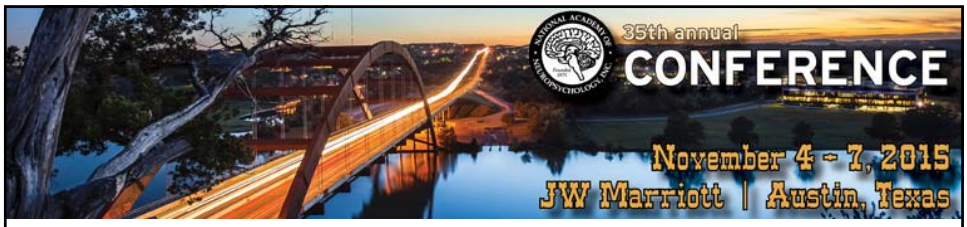
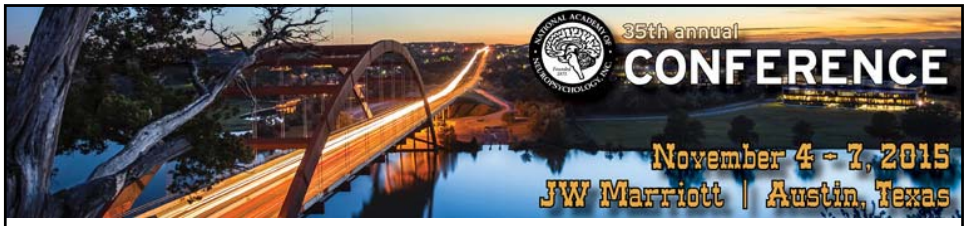


Table 1. Demographic Characteristics and Cognitive Test Results from the Health and Aging Brain Among Latino Elders Study Sample According to Estimated Glomerular Filtration Rate

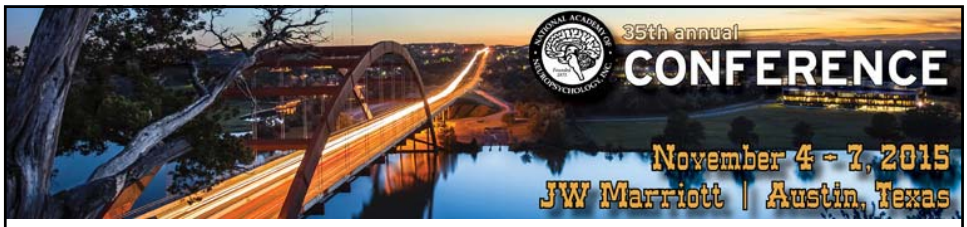
Characteristics and Tests	Total Sample	<45 mL/min per kg², n = 14	45–59 mL/min per kg², n = 20	≥60 mL/min per kg², n = 403
Age, mean ± SD	61.3 ± 8.3	71.4 ± 8.1	68.9 ± 8.5	60.4 ± 7.7
Education, years, mean ± SD	7.7 ± 4.3	6.7 ± 5.7	7.6 ± 3.4	7.7 ± 4.3
Female, %		76	75	64
Estimated glomerular filtration rate 60 mL/min per 1.73 m², mean ± SD	86.3 ± 17.0	36.5 ± 7.5	52.1 ± 3.9	89.8 ± 12.3
Mini-Mental State Examination score, mean ± SD	25.5 ± 4.0	21.5 ± 5.9	25.9 ± 2.5	25.7 ± 3.7
TMT Part A, seconds, mean ± SD[a]	63.6 ± 32.4	113.3 ± 53.8	65.9 ± 22.3	61.7 ± 30.6
TMT Part B, seconds, mean ± SD[a]	161.3 ± 79.0	193.7 ± 84.9	198.4 ± 81.2	158.9 ± 78.4
Wechsler Memory Scale, third edition, logical memory sclore, mean ± SD	18.0 ± 9.0	12.4 ± 11.7	17.7 ± 8.0	18.5 ± 8.9
Consortium for the Establishment of Registry for Alzheimer's Disease recall score, mean ± SD	4.8 ± 2.4	2.7 ± 2.3	3.3 ± 2.1	4.9 ± 2.3
CLOX1 score, mean ± SD	10.7 ± 2.5	8.2 ± 2.8	10.7 ± 2.1	10.9 ± 2.4
CLOX2 score, mean ± SD	13.1 ± 1.7	11.1 ± 3.2	12.8 ± 1.6	13.2 ± 1.6
FAS score, mean ± SD	24.0 ± 10.4	21.5 ± 14.9	23.6 ± 11.4	24.3 ± 10.2
Animal naming, mean ± SD	15.4 ± 4.7	12.0 ± 5.3	14.0 ± 4.1	15.6 ± 4.6
Executive interview score, mean ± SD[a]	9.8 ± 4.7	13.1 ± 4.5	10.9 ± 5.7	9.6 ± 4.6

SD = standard deviation; TMT = Trail-Making Test; CLOX = clock drawing; FAS = functional assessment score.
All scores are raw values.
[a] Higher scores indicate poorer performance; for all other tests, higher scores indicate better performance.

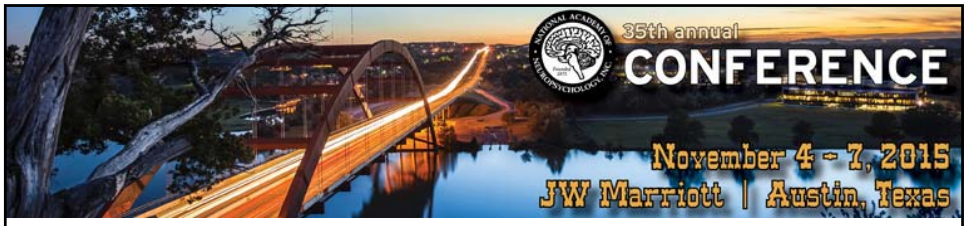


Summary

- Mexican Americans
  - Higher prevalence of DM, depression and comorbid DM + Dep
  - Higher rates of kidney disease
  - Lower frequency of APOE4
  - Younger age of MCI (same discrepancy as age difference of DM onset)
  - "Traditional" risk factors may not contribute to AD and MCI in same manner as among non-Hispanic whites

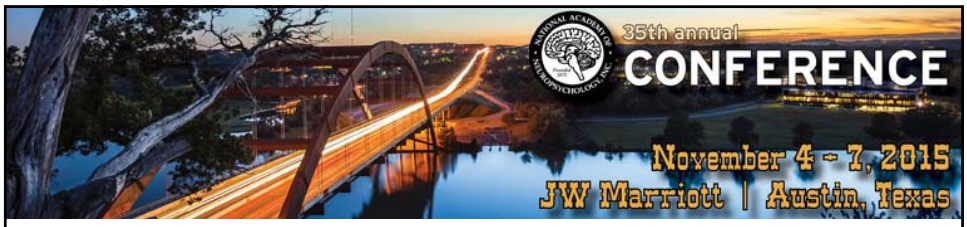


PROTEOMICS OF AD AND MCI AMONG MEXICAN AMERICANS



Why examine proteomics

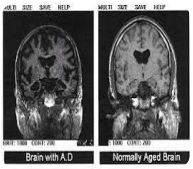
- Our lab has focused on the identification of a blood test to detect AD in primary care settings as the 1st step in a multi-stage diagnostic process (similar to cancer, CVD)



Current state-of-the-art diagnosis


PCP Referral


Specialist Exam



Brain MRI


Blood Work


NPSY Testing


35th annual
CONFERENCE
November 4 - 7, 2015
JW Marriott | Austin, Texas
Current state-of-the-art diagnosis
$$$$
PCP Referral
Specialist Exam
Brain with A.D
Normally Aged Brain
Brain MRI
Blood Work
NPSY Testing
DIAGNOSIS


35th annual
CONFERENCE
How is Alzheimer's disease diagnosed?
November 4 - 7, 2015
W Marriott | Austin, Texas
Screen Positive?
Yes
No
Screen again
next year


35th annual
CONFERENCE
How is Alzheimer's disease diagnosed?
November 4 - 7, 2015
W Marriott | Austin, Texas
How to screen 40 million Americans?
Screen Positive?
Yes
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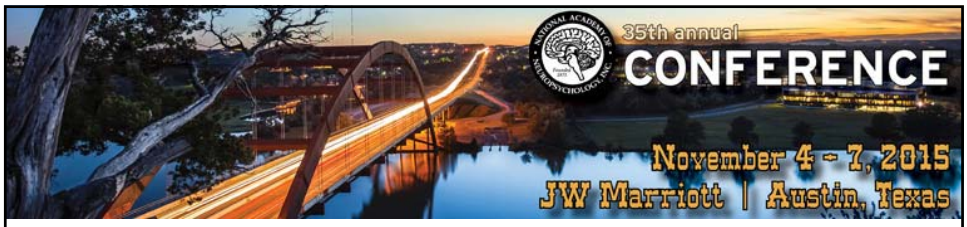
CONFERENCE
How is Alzheimer's disease diagnosed?
November 4 - 7, 2015
W Marriott | Austin, Texas
How to screen 40 million Americans?
Screen Positive?
Yes
No
Screen again
next year

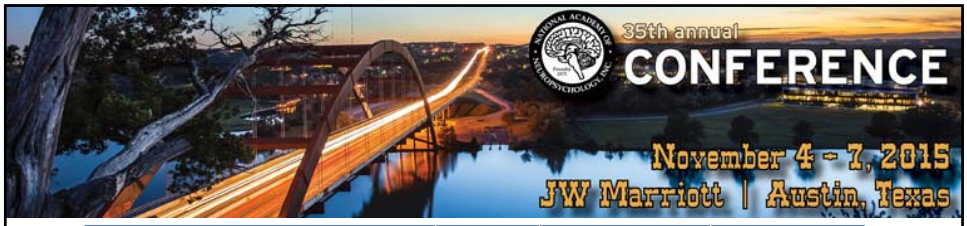
What's new in diagnostics?

- Neuroimaging and CSF methods accurate
- Not viable for front-line screening by PCPs
- **A blood test for AD?**
  - Screening in primary care clinics
  - Access to available treatments
  - Increase access to clinical trials



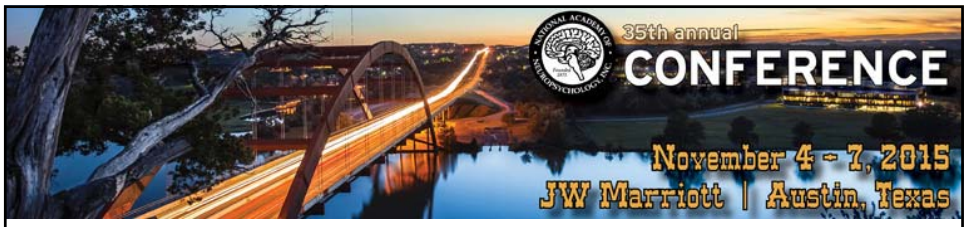
Summary of Prior Work

- Discovery of algorithm on Luminex platform
- Validation across cohorts (TARCC, ADNI, others)
- Validation across platforms (ECL)
- Validation across species and tissue type



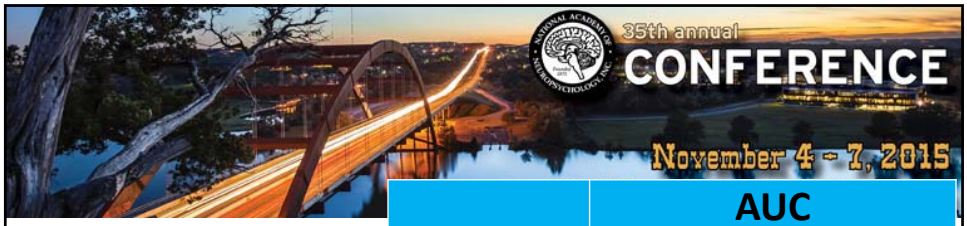
Diagnostic Accuracy of Blood Markers of AD	AUC	Sensitivity	Specificity
108 protein algorithm	0.95	0.94	0.84
30-protein algorithm	0.94	0.89	0.85
Serum-Plasma algorithm	0.89	0.75	0.91
CSF biomarker accuracy	0.92	0.84	1.00
21-protein version	0.98	0.90	0.90

O'Bryant 2010, 2011, 2011, 2014, 2014



Summary of Prior Work

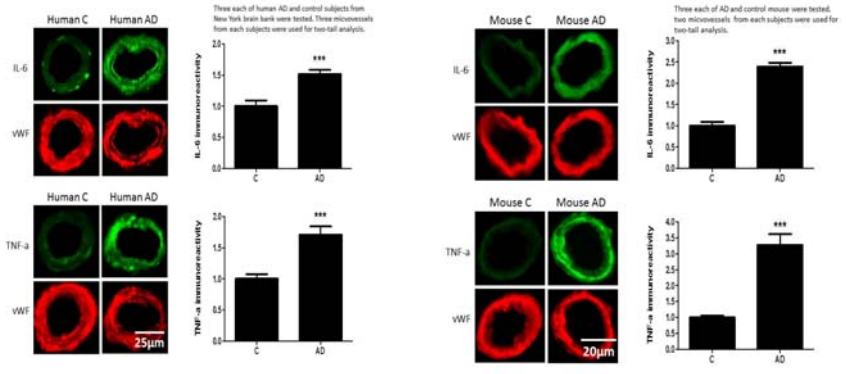
- Cross-validation Among Mexican Americans
  - Luminex platform – AUC = 0.88 (TARCC)
  - ECL platform– AUC = 0.88 (HABLE)
  - MCI using ECL platform – AUC = 0.90 (HABLE)



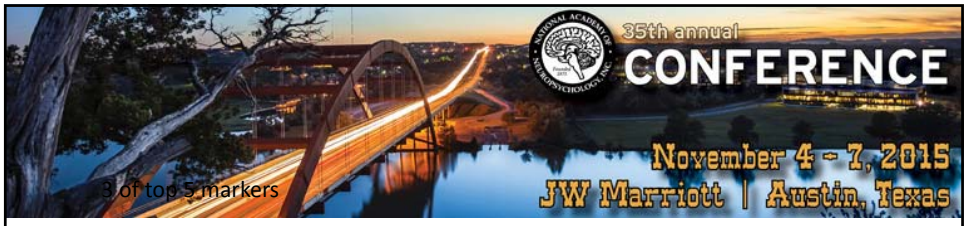
Normal Cognition vs. Alzheimer's Disease

	AUC
HABLE	.90
TARCC	.96
Panama	.96
UTSW ADC	.84
All Merged N=1,500	.90

Cross-validating in human and mouse brain microvessels



O'Bryant et al in prep

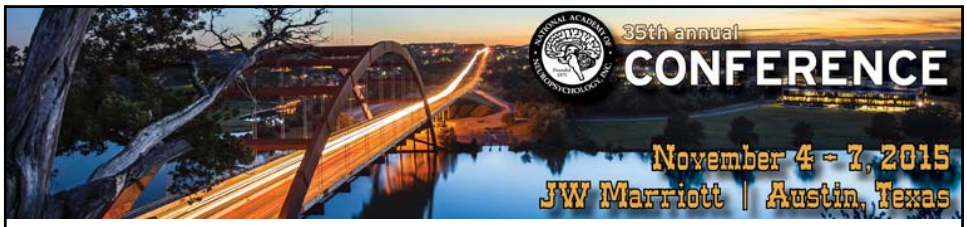


3 of top 5 markers

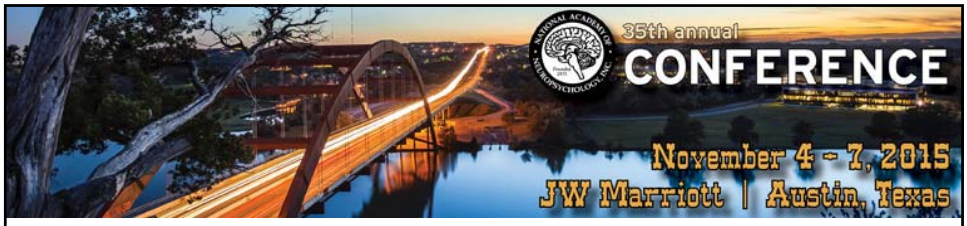
Classification Table[a]

			Predicted		
			diagnosis		
	Observed		0	1	Percentage Correct
Step 1	diagnosis	0	8	1	88.9
		1	1	8	88.9
	Overall Percentage				88.9

a. The cut value is .500



Blood Profile of AD and MCI among Mexican Americans



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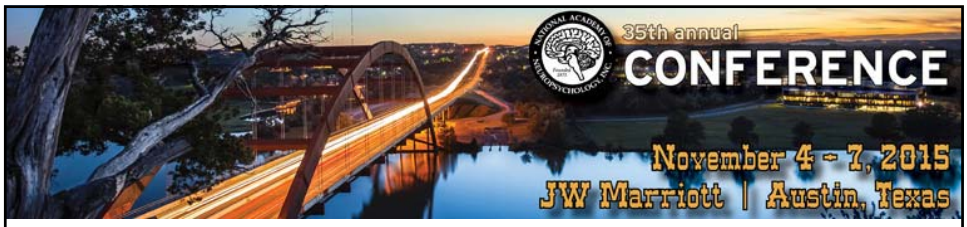
DOI 10.3233/JAD-122074
IOS Press

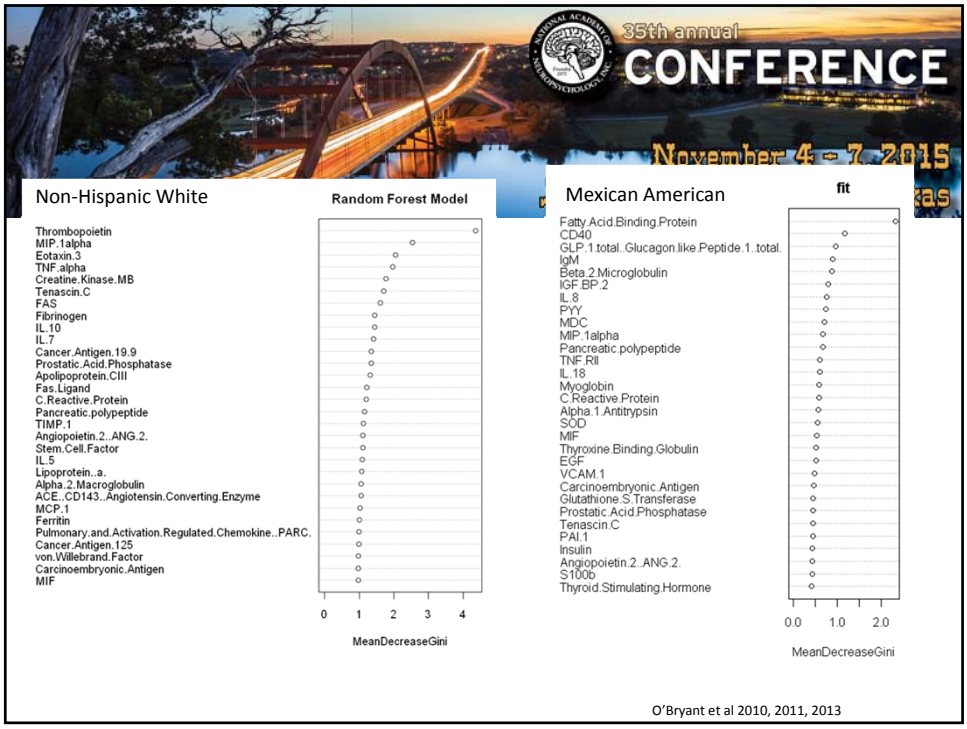
Biomarkers of Alzheimer's Disease Among Mexican Americans

Sid E. O'Bryant[a,b,*], Guanghua Xiao[c], Melissa Edwards[a,d], Michael Devous[e], Veer Bala Gupta[f,g], Ralph Martins[f,g], Fan Zhang[h] and Robert Barber[b,i] for the Texas Alzheimer's Research and Care Consortium (TARCC)[1]

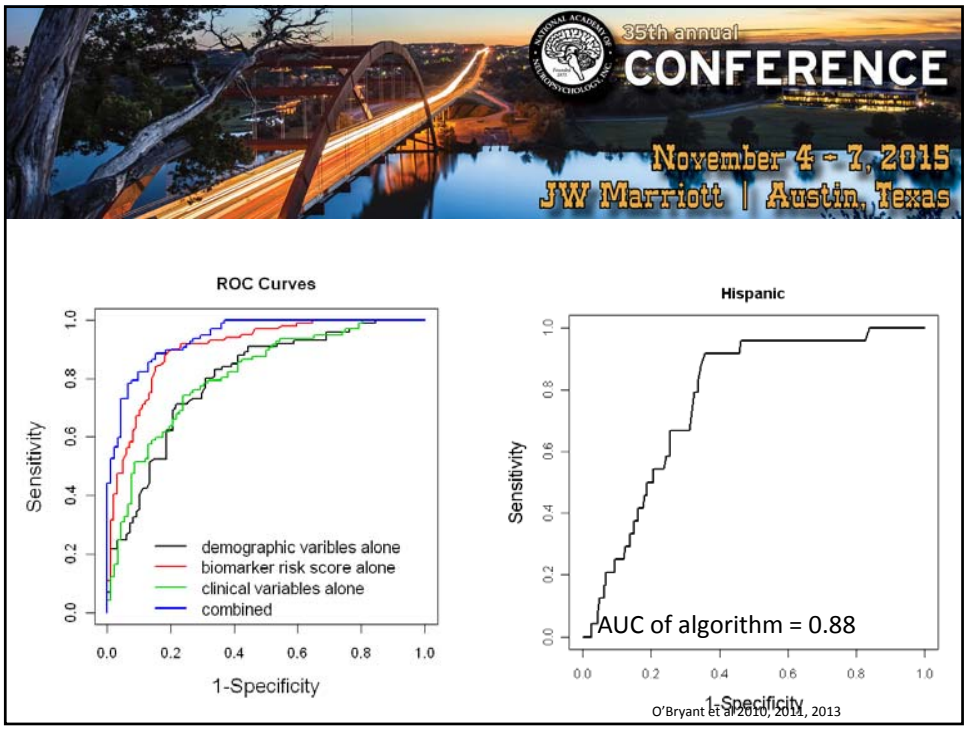


Blood screen among Mexican Americans

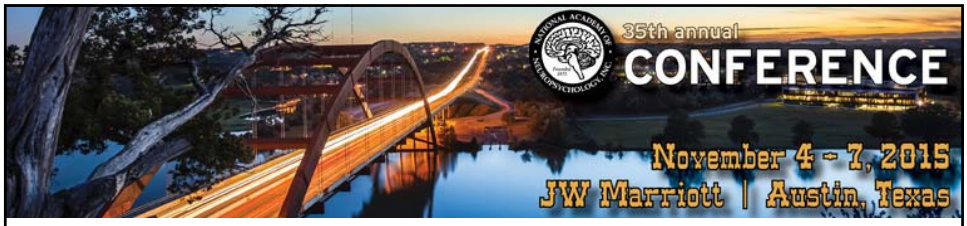
- Same biomarkers assayed from serum of 363 Mexican Americans from the TARCC study
  - AD n=49
  - NC n=314



O'Bryant et al 2010, 2011, 2013



O'Bryant et al 2010, 2011, 2013



Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-150553
IOS Press

Molecular Markers of Amnestic Mild Cognitive Impairment among Mexican Americans

Melissa Edwards[a], James Hall[b,c], Benjamin Williams[d], Leigh Johnson[c,e] and Sid O'Bryant[c,e,*]

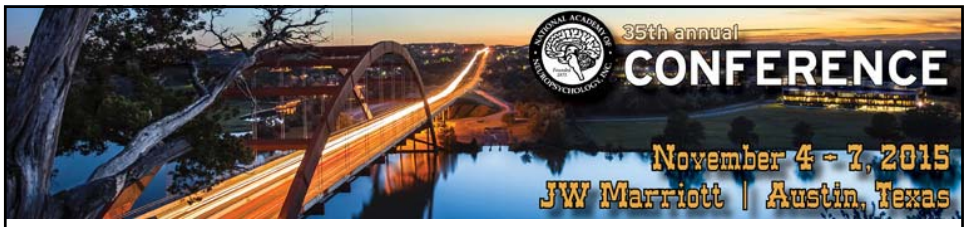
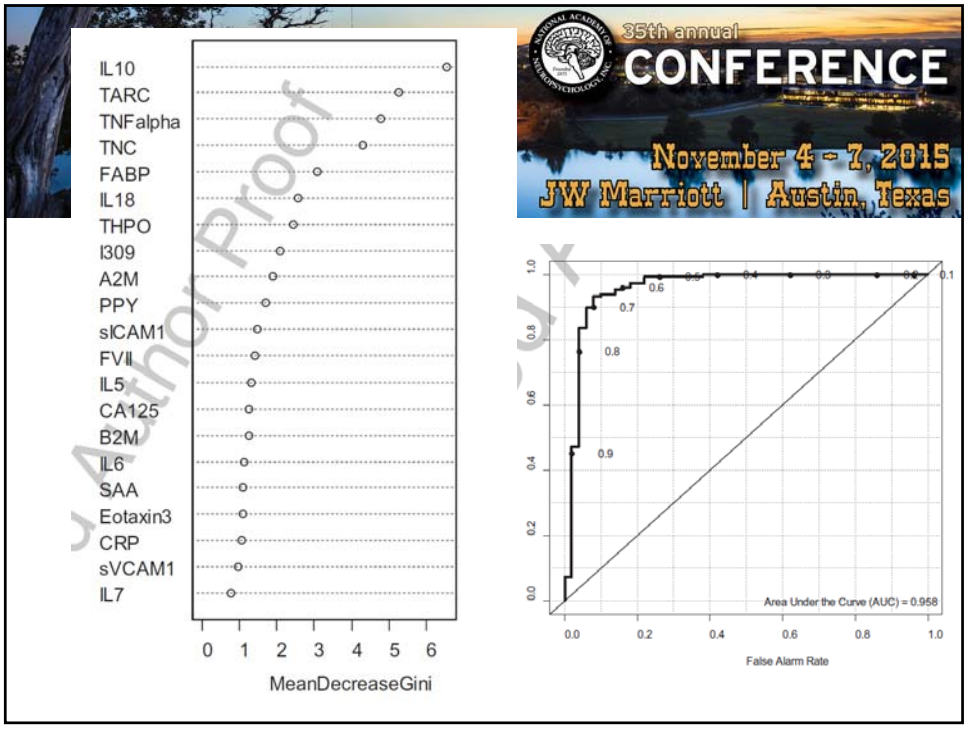
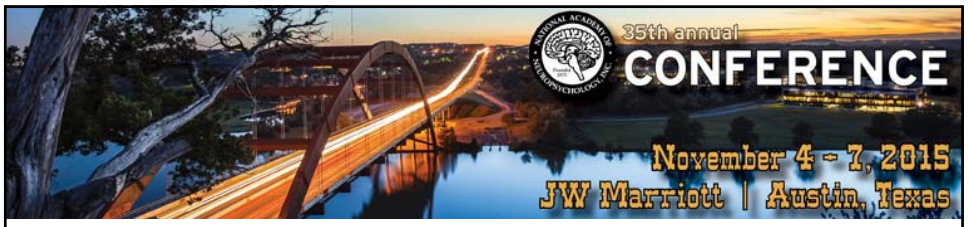


Table 1
Demographic characteristics

	aMCI Mean (SD) $n = 73$	Normal Control Mean (SD) $n = 211$	p value
Gender (% male)	21%	36%	
Age	66.30 (8.45)	58.75 (6.29)	<0.001
Education	6.96 (4.79)	8.94 (4.41)	0.001
MMSE	23.64 (3.69)	27.13 (2.40)	<0.001
CDR SB	1.21 (0.82)	0.00 (0.00)	<0.001

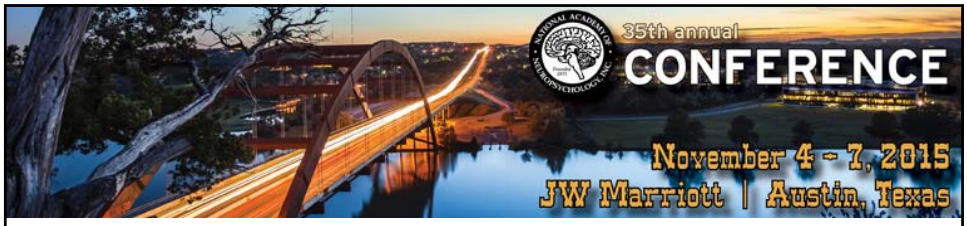
*$p < 0.05$.





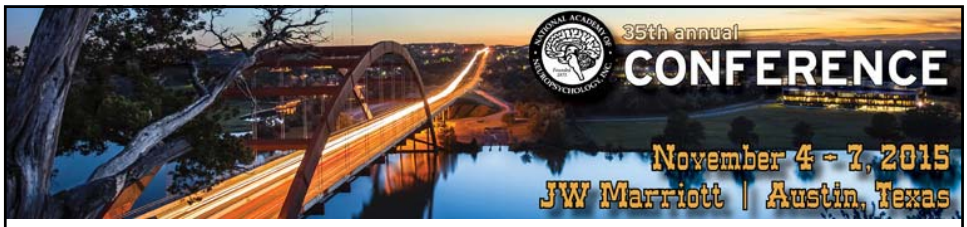
MCI vs. AD profiles

- AD profile is metabolic in nature
- MCI is inflammatory/vascular in nature

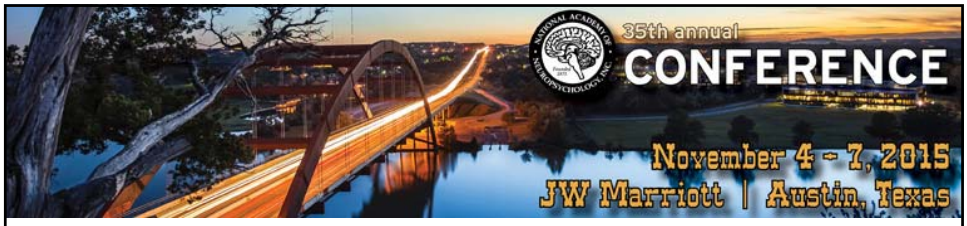


Could this have therapeutic implications?

	<=60 Inf+ Mean age = 58	>60 Inf+ Mean age = 73
WMS3 LM1	5.8	8.4
WMS3 LM2	5.3	6.3

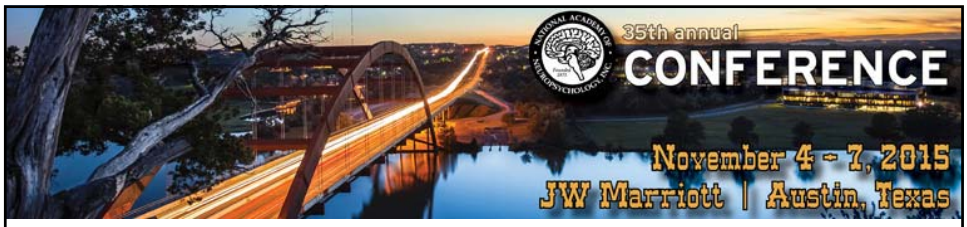


What about combining comorbidities with proteomics?



Depression + Inflammation?

	DepE Positive			DepE Negative		
	Low Inf	Middle Inf	High Inf	Low Inf	Middle Inf	High Inf
WMS III LM1	10.3(3.1)	9.0(3.7)	8.5(3.7)	11.1(2.8)	10.7(3.2)	9.4(3.8)
WMS III LM2	10.2(3.1)	8.6(3.5)	7.7(3.8)	11.3(2.9)	11.0(3.2)	9.4(3.8)
CERAD List Recall	9.2(2.6)	8.0(2.7)	6.4(2.8)	8.5(2.6)	8.6(2.6)	7.6(3.4)

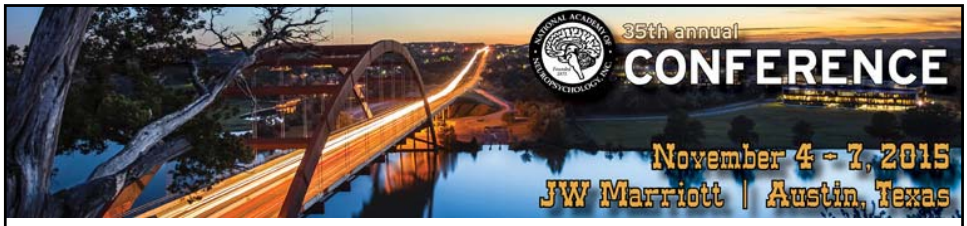


Proteomic Profile of CKD-Related MCI

Table 3. Sensitivity and Specificity of Biomarker Profile in Detecting Mild Cognitive Impairment (MCI) and Pre-MCI in Individuals with Chronic Kidney Disease (CKD)

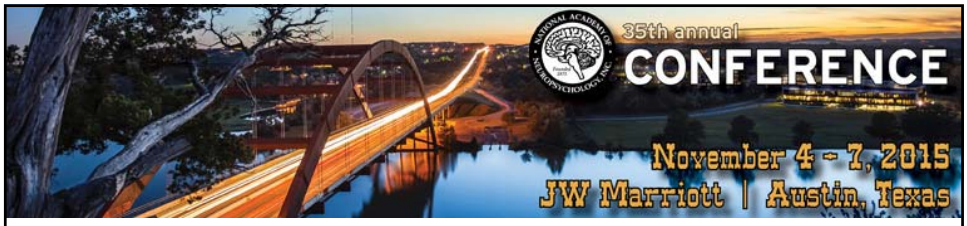
Diagnostic Category	Sensitivity (95% CI)	Specificity (95% CI)
CKD and MCI	0.86 (0.58–0.98)	1.00 (0.78–1.00)
CKD no MCI	0.24 (0.14–0.35)	0.98 (0.81–0.88)
CKD and pre-MCI	1.00 (0.71–1.00)	1.00 (0.50–1.00)
CKD no pre-MCI	0.00 (0.00–0.00)	1.00 (0.00–0.96)

CI = confidence interval.



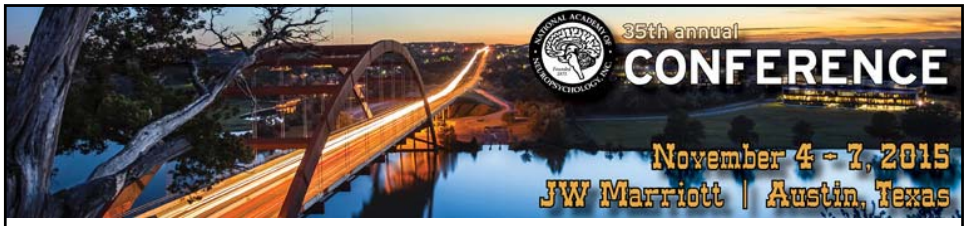
Summary

- Clinical –
  - Do not use term "dementia"
  - Clinical interview will take longer
- Norms
  - New norms will be published soon
  - Education is a key factor for normative stratification



Summary

- Comorbidities –
  - Higher prevalence of DM, dep, and other medical factors
  - Lower frequency of APOE4 genotype
- Proteomics -
  - Proteomic profile of AD is metabolic but MCI is inflammatory
  - Proteomic considerations may need to be condition specific
  - May assist in precision-based medicine for treating MCI/AD



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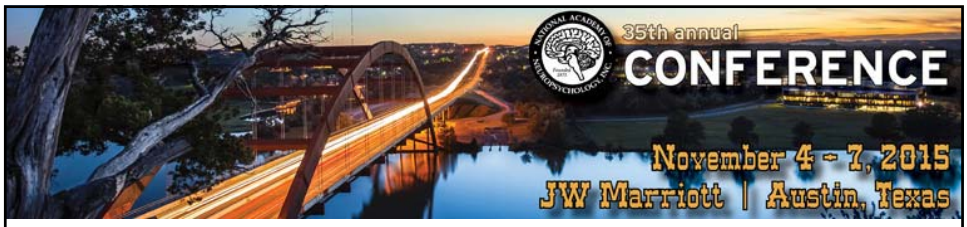
- Kim Brown



Thank You!