

# Impact of Study Partner Type on AD Progression

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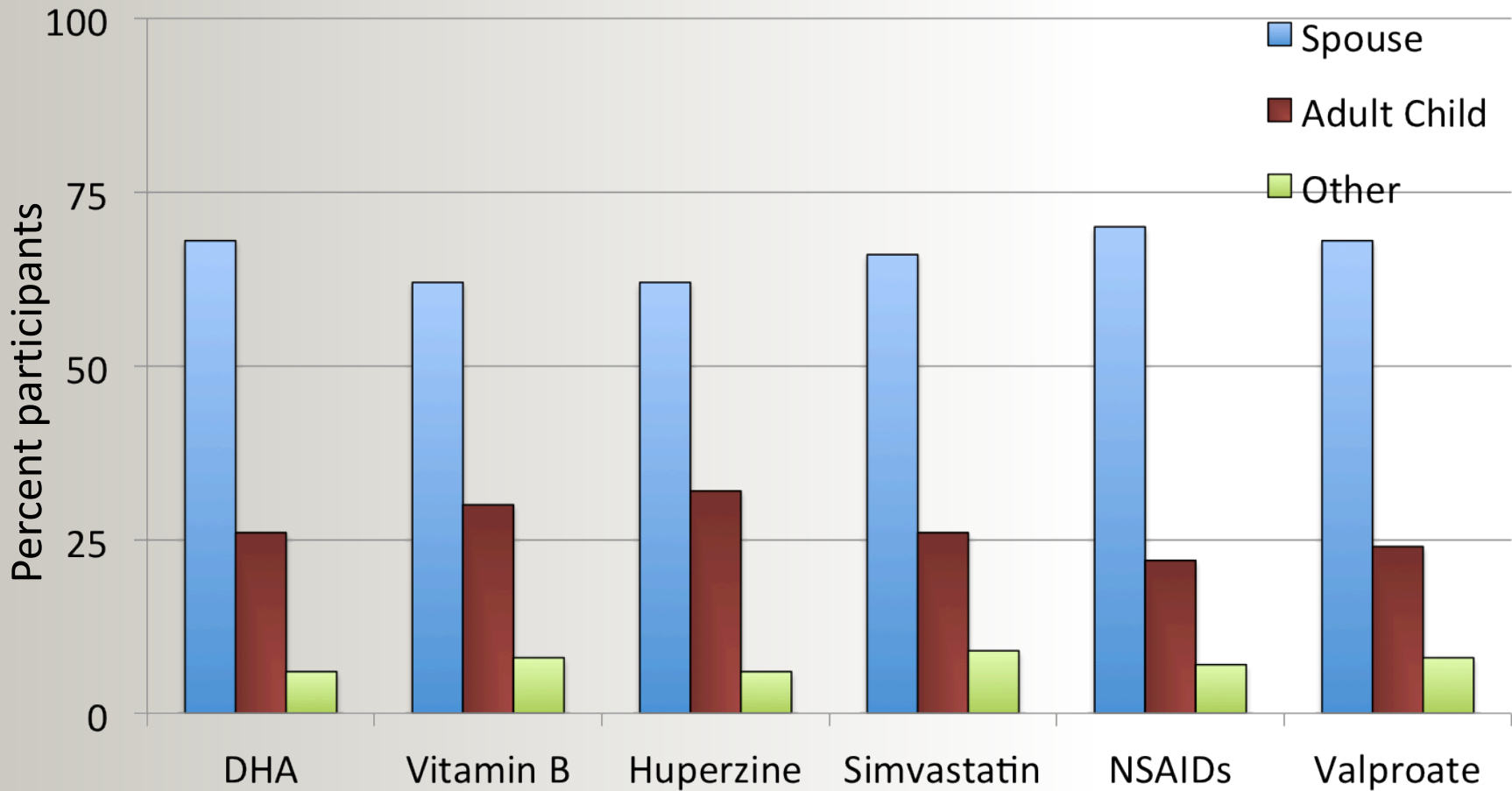
# Disclosures

- Site investigator on clinical trials sponsored by the Alzheimer's Disease Cooperative Study (NIA), Janssen AI, Pfizer, Bristol Myers Squibb, Genentech, Avanir, Biogen Idec.
- Principal investigator of single site study sponsored by John Douglas French Foundation for which the medical food is generously donated by Accera Inc.
- Consultant to Avanir Pharmaceuticals, Phloronol, Inc (more than 12 months prior)
- Funding: NIA AG016570, NACC JIA

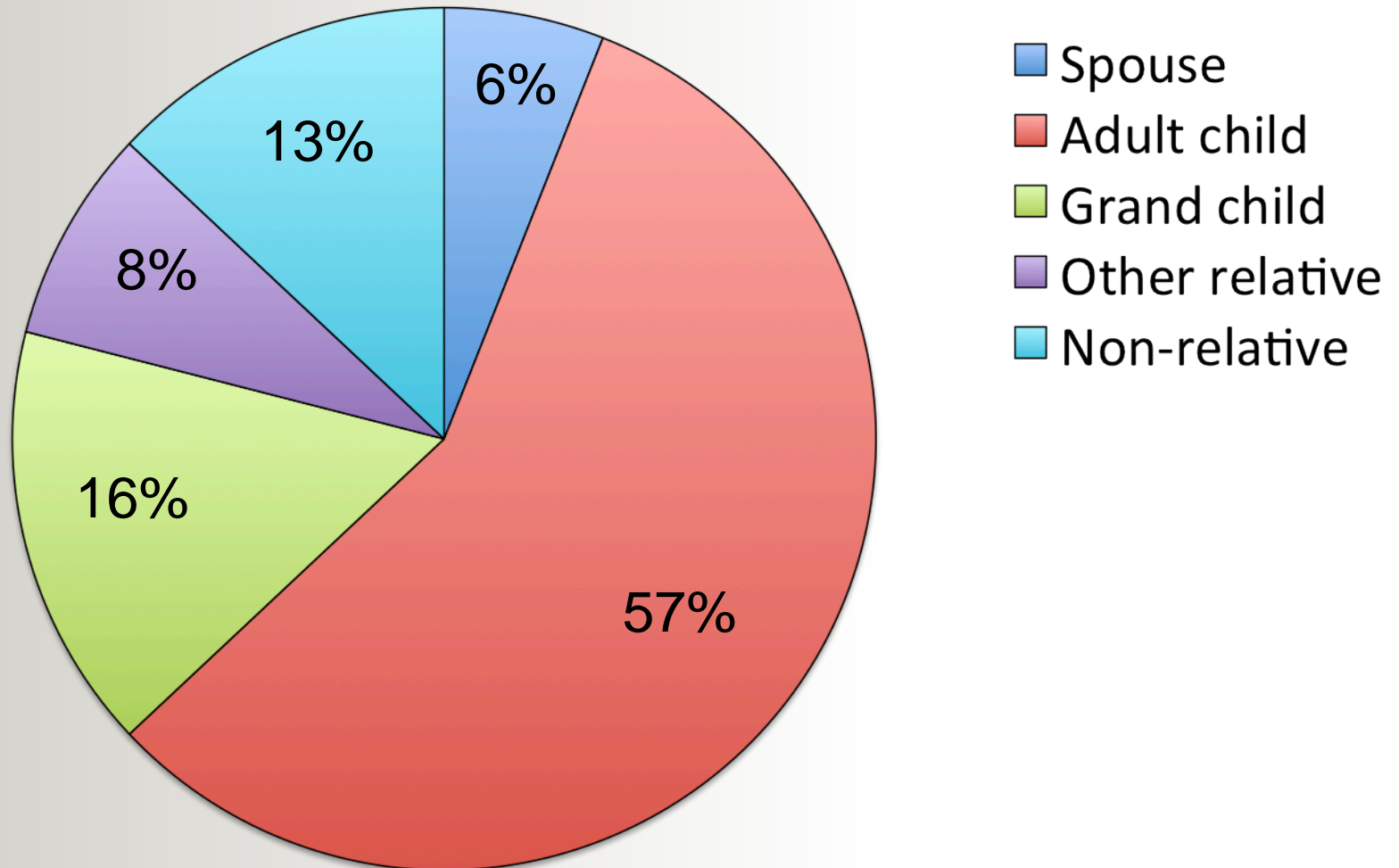
# Study Partner Role in AD Trials

- Critical decision-maker, whether to enroll
- Ensure visit and drug compliance
- Primary informant for trial outcomes
  - AEs / SAEs
  - Efficacy measures including co-primary outcomes for registration trials

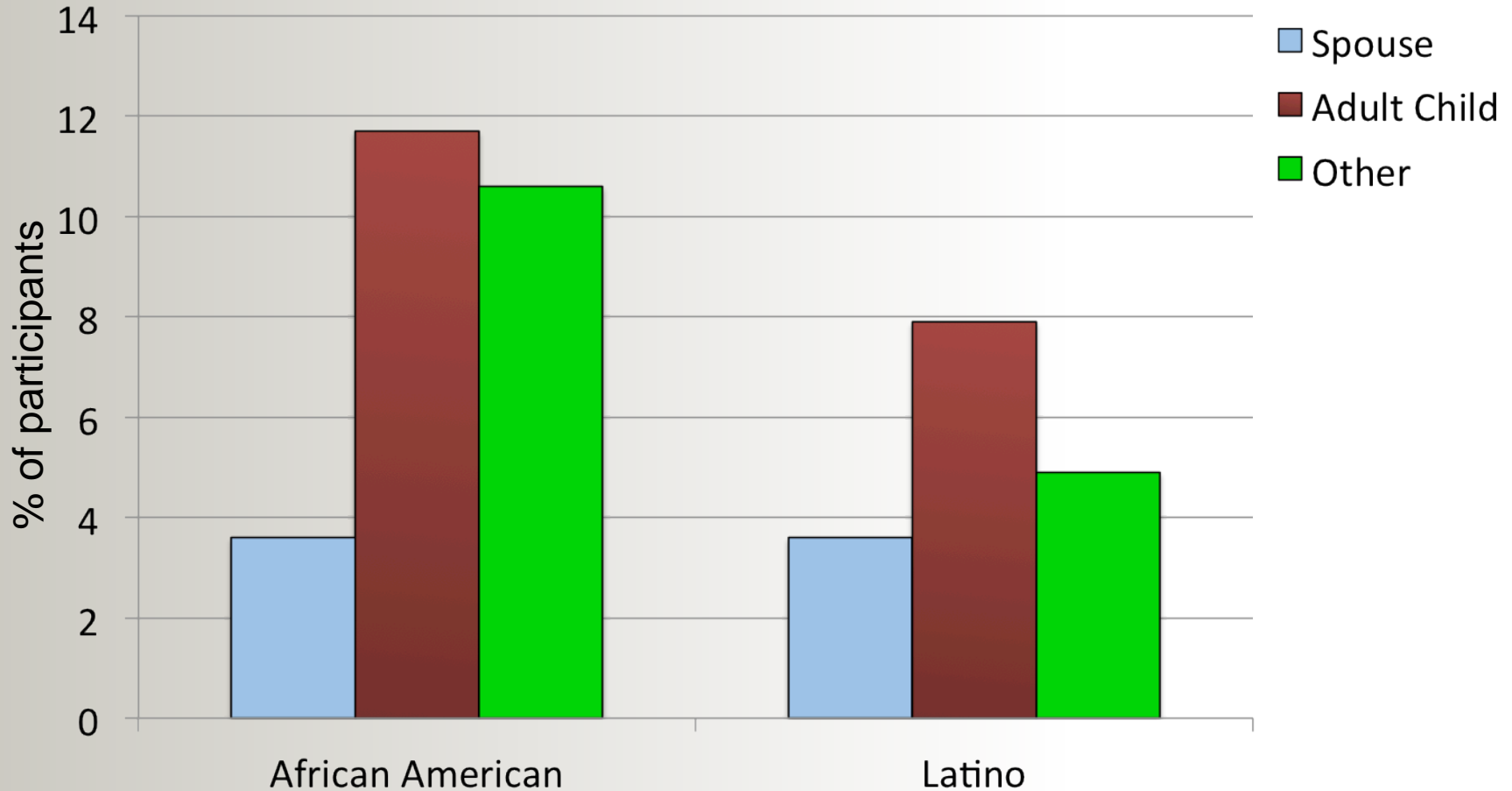
# ADCS Trial Study Partners



# AD Caregiver Epidemiology



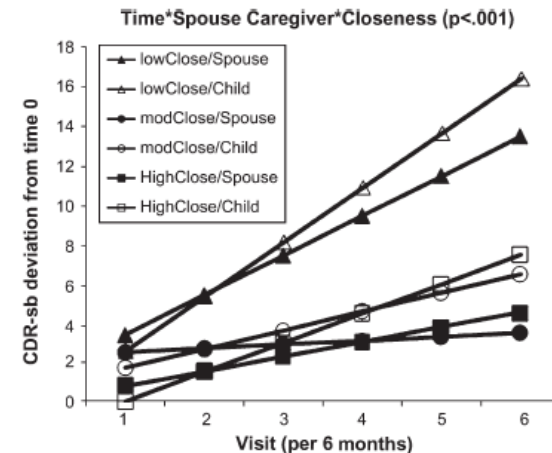
# Minority AD Trial Participants





# Cache County Study

- Examined impact of caregiver relationship and relationship closeness of rate of disease progression (CDR-SB)
  - 167 possible/probable AD patient/caregiver dyads
- Relationship closeness ( $p=0.05$ ) and spousal status ( $p=0.01$ ) were associated with slower decline





# NACC UDS Study

- Rationale: differences in rate of progression could impact trial planning or results
- Hypothesis: probable AD participants with an adult child study partner progress more rapidly than those with a spouse

# Methods

- Sample
  - Age = 55-90
  - Global CDR = 0.5 or 1.0
  - MMSE = 14-26 (inclusive)
  - $\geq 2$  follow up visits with at least 2/3 outcomes of interest
  - Exclusion
    - Change in study partner
    - Change in diagnosis

# Methods

- Outcomes of interest
  - MMSE (Folstein 1975); Range 0-18 (higher = more cognitively impaired)
  - FAQ (Pfeffer 1982); Range 0-30 (higher = more functionally impaired)
  - CDR-SB (Morris 1993); Range 0-18 (higher = more globally impaired)
- Two-year annualized change

# Progression Models

- Examined predictors of disease progression using multiple regression models
- 2 samples:
  - All available data from participants meeting criteria
  - Propensity matching case-control

# Propensity Matching

- Technique to remove bias in observational studies (randomization is not feasible)
- For each participant, a propensity score is calculated (multiple logistic regression model):

$$e(x_i) = \Pr(D_i = 1 | X_i = x_i)$$

$e_i$  = propensity score

$D_i$  = study partner type

$x_i$  = set of covariates (i.e. education, race, ethnicity, baseline MMSE, baseline CDR-SB, baseline NPI, hachinski score, presence of anti-AD medications)

- To be considered a match, two scores needed to score within 0.05.

# Propensity Matching Results

- When age or gender were included in the model, insufficient matching occurred to permit examination
- The model including education, race, ethnicity, baseline MMSE, baseline CDR-SB, baseline NPI, hachinski score, presence of anti-AD medications yielded satisfactory matching :
  - 1.76 participants with a spousal partner for every participant with an adult child partner

# Demographics

Characteristic	All available data			Matched Sample		
	Adult child partner	Spouse Partner	P value ( $\chi^2$ or t-test)	Adult child partner	Spouse Partner	P value ( $\chi^2$ or t-test)
N (%)	384 (25.7)	1111 (74.3)		318 (36.3)	559 (63.7)	
Age, mean years $\pm$ SD	78.6 $\pm$ 6.2	73.2 $\pm$ 8.0	<0.0001	78.8 $\pm$ 6.3	73.7 $\pm$ 7.79	<0.0001
Female, n (%)	322 (83.9)	377 (33.9)	<0.0001	266 (83.7)	195 (34.9)	<0.0001
Minority race, n (%)	93 (24.4)	106 (9.5)	<0.0001	64 (20.1)	87 (15.6)	0.08
Latino ethnicity, n (%)	53 (13.9)	33 (3.0)	<0.0001	28 (8.8)	30 (5.4)	0.05
Education, mean years $\pm$ SD	13.1 $\pm$ 3.5	15.2 $\pm$ 3.1	<0.0001	13.6 $\pm$ 3.0	14.1 $\pm$ 3.1	0.03

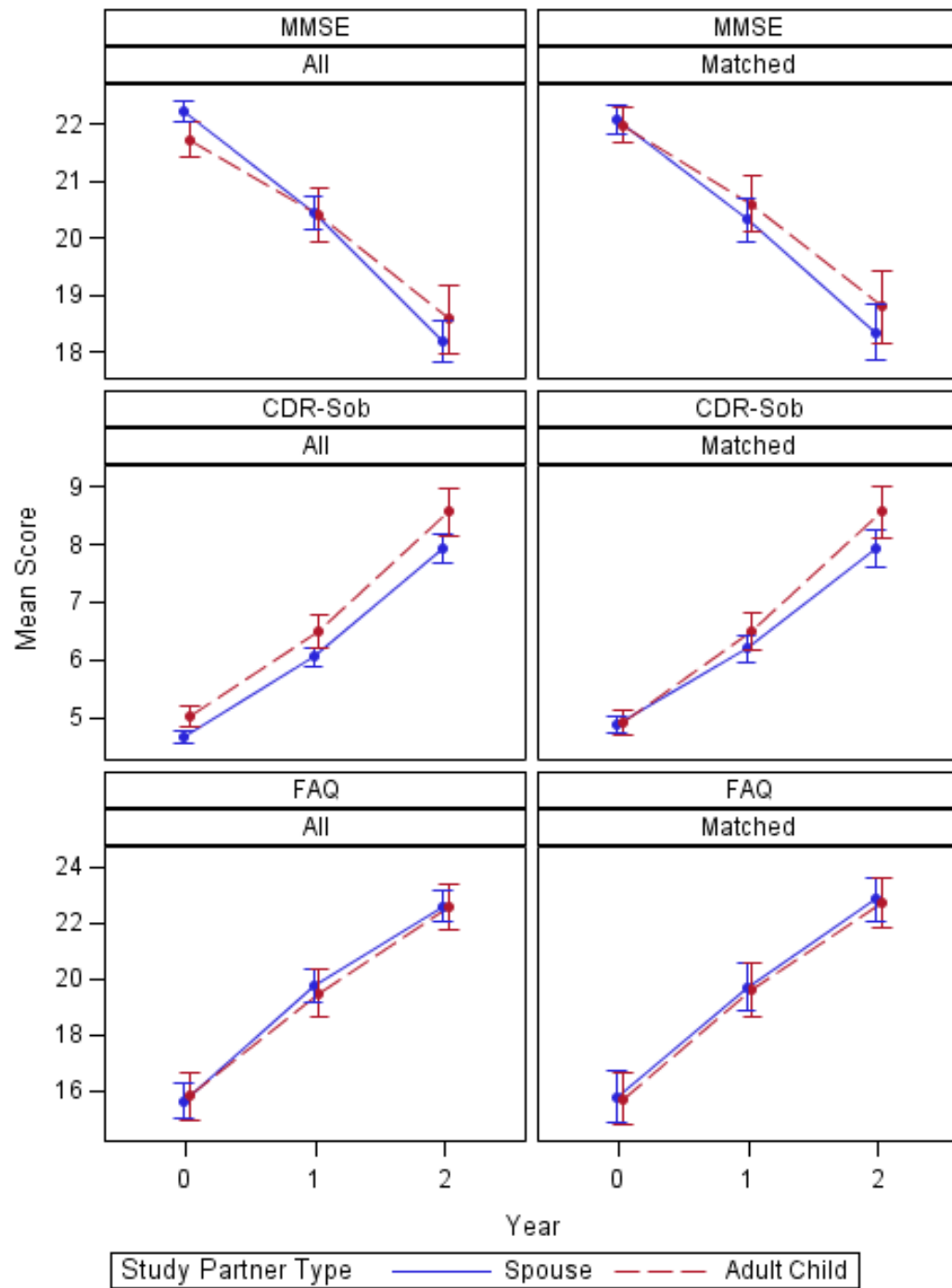
# Baseline Scores

Baseline Characteristic	All available data			Matched Sample		
	Adult child	Spouse	P value ( $\chi^2$ or t-test)	Adult child	Spouse	P value ( $\chi^2$ or t-test)
Global CDR, mean $\pm$ SD	0.8 $\pm$ 0.2	0.8 $\pm$ 0.3	NS	0.8 $\pm$ 0.2	0.8 $\pm$ 0.3	NS
CDR-SB, mean $\pm$ SD	5.0 $\pm$ 1.9	4.7 $\pm$ 1.7	<0.001	4.9 $\pm$ 1.9	4.9 $\pm$ 1.8	NS
MMSE, mean $\pm$ SD	21.7 $\pm$ 3.1	22.2 $\pm$ 3.2	<0.01	22.0 $\pm$ 2.9	22.1 $\pm$ 3.1	NS
FAQ, mean $\pm$ SD	15.8 $\pm$ 7.1	15.6 $\pm$ 7.4	NS	15.7 $\pm$ 7.2	15.8 $\pm$ 7.4	NS
NPI-Q, mean $\pm$ SD	4.2 $\pm$ 4.1	3.9 $\pm$ 3.8	NS	4.1 $\pm$ 4.0	4.2 $\pm$ 4.1	NS



## Significant Predictors; Propensity Matched Sample

Variable	CDR-SB, estimate (95% CI)	MMSE, estimate (95% CI)	FAQ, estimate (95% CI)
Adult child partner (vs. spouse)	-0.05 (-0.26, 0.32)	0.28 (-0.19, 0.75)	-0.34 (-1.04, 0.42)
Female partner (vs. male)	0.19 (-0.10, 0.49)	-0.14 (-0.35, 0.62)	0.09 (-0.64, 0.82)
Female (vs. male)	0.40 (0.08, 0.71)*	-0.25 (-0.76, 0.26)	0.50 (-0.30, 1.30)
Caucasian (vs. non-Caucasian)	0.07 (-0.22, 0.36)	-0.04 (-0.50, 0.42)	0.38 (-0.40, 1.15)
Latino (vs. non-Latino)	-0.10 (-0.54, 0.34)	0.61 (-0.09, 1.32)	-0.49 (-1.66, 0.69)
Education	0.04 (-0.01, 0.06)	-0.01 (-0.04, 0.07)	0.11 (0.01, 0.21)*
Age	-0.002 (-0.01, 0.02)	0.04 (0.01, 0.06)*	-0.01 (-0.03, 0.05)
Baseline score	0.10 (0.04, 0.16)*	-0.01 (-0.07, 0.05)	-0.22 (-0.26, -0.19)*



# Limitations

- Propensity matching was unsuccessful when model included age and gender
- NACC doesn't require the primary caregiver to serve as study partner
- An ideal design includes informant-dependent and –independent measures of each of
  - Cognition
  - Function
  - Global performance

# Sample Bias?

Sample	Finding
ADCS trials	Adult child study partners = progress more slowly (trend)
NACC UDS	No difference
Cache County	Patient with adult child caregivers = progress more rapidly

## Differences in study requirements

- Visit frequency
- Visit location
- Recruitment

# Summary

- Study partner type did not impact rate of AD progression among NACC participants on common trial outcome measures
- Support the enhanced enrollment of nonspousal AD caregiver-patient dyads
  - No need for stratified enrollment
  - No need for analytic adjustment

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