Schizophrenia and Aging: Myths and Reality

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Potential Conflicts of Interest

- **Donation of antipsychotic medications for an NIMH-funded RO1: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen**

Self-Assessment Question 1

Which of the following statements is true?

A. Rate of age-related cognitive decline in late-onset schizophrenia does not differ from that in normal subjects.

B. Remission of schizophrenia in late life appears independent of age or chronicity of illness

C. Positive symptoms in late-onset schizophrenia are as prevalent as in early-onset schizophrenia.

D. Female gender is over-represented among patients with late-onset schizophrenia

E. All of the above

Self-Assessment Question 2

Compared to early-onset schizophrenia, which of the following is true of late-onset schizophrenia?

A. Negative symptoms are more severe
B. Paranoid subtype is more prevalent
C. A smaller percentage of patients have ever been married
D. All of the above
E. None of the above

Self-Assessment Question 3

Which of the following statements is true of neuropsychological findings in patients with late-onset schizophrenia?

A. A wide range of cognitive deficits have been reported
B. Compared to patients with early-onset schizophrenia, less severe deficits in learning and executive functions characterize patients with late-onset schizophrenia
C. The overall pattern of deficits is similar to that seen in early-onset schizophrenia
D. All of the above
E. None of the above

Self-Assessment Question 4
Which of the following is true regarding treatment of late-onset schizophrenia?

A. The cumulative incidence of tardive dyskinesia with conventional antipsychotics is low in elderly patients.
B. Risperidone has been shown to be superior to olanzapine in treating positive and negative symptoms of late-onset schizophrenia.
C. Cognitive Behavioral Social Skills Training has been shown to improve cognitive insight and socialization in older people with schizophrenia
D. All of the above
E. None of the above

Self-Assessment Question 5

Which of the following are long-term adverse effects of atypical antipsychotics?

A. Weight gain
B. Type 2 diabetes mellitus
C. Dyslipidemia
D. Increase in strokes and mortality in dementia patients
E. Any of the above

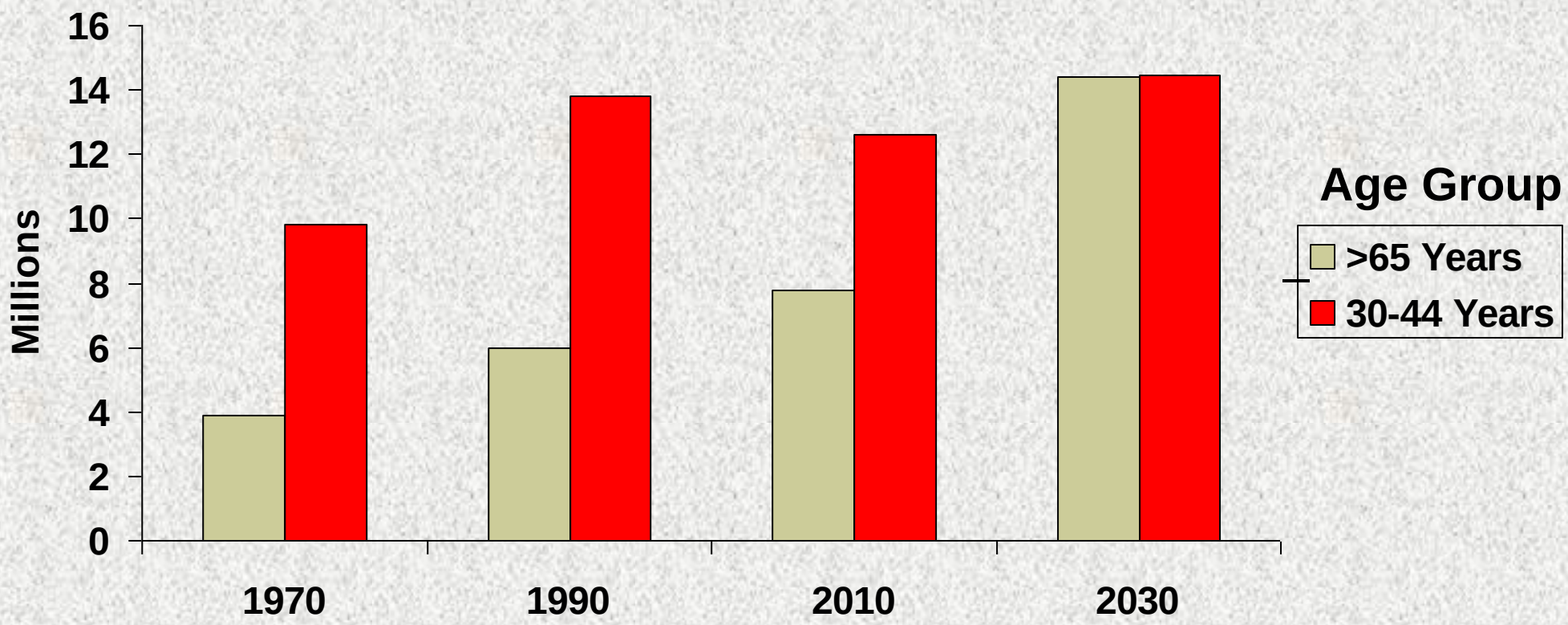
Major Points

- Schizophrenia can manifest for the first time after age 40
- Course of schizophrenia in late life is generally characterized by persistence of negative symptoms, absence of rapid cognitive decline, and modest improvement in positive symptoms
- Very late-onset schizophrenia-like psychosis (with onset after age 60) is a heterogeneous syndrome that includes psychosis of dementia or of other medical conditions, substance use, or psychosis NOS
- Other conditions in differential diagnosis include delusional disorder and psychosis associated with mood disorders
- Treatment with atypical antipsychotics is associated with symptomatic improvement but also potentially hazardous metabolic side effects offset by lower rates of tardive dyskinesia and other extra-pyramidal symptoms
- Psychosocial approaches have been shown to improve functioning in older patients with schizophrenia.

OUTLINE

- Introduction
- Course of Schizophrenia in Late Life
- Middle-Age-Onset Schizophrenia
- Very Late-Onset Schizophrenia-like Psychosis
- Pharmacologic & Psychosocial Treatments

Estimated Numbers of People with Psychiatric Disorders in USA



Jeste DV et al., *Arch Gen Psychiatry*, 56:848-853, 1999

Late-Life Course of Schizophrenia

- Over 1,200 middle-aged and older people with schizophrenia studied at UCSD since 1987
- Relatively stable and non-deteriorating course
- Improvement in Tx adherence and in psychotic symptoms, with fewer relapses, with aging
- Rate of age-related cognitive change is similar in patients and normal subjects
- There is age-related decline in physical health but improvement in mental health (self-rated quality of life)

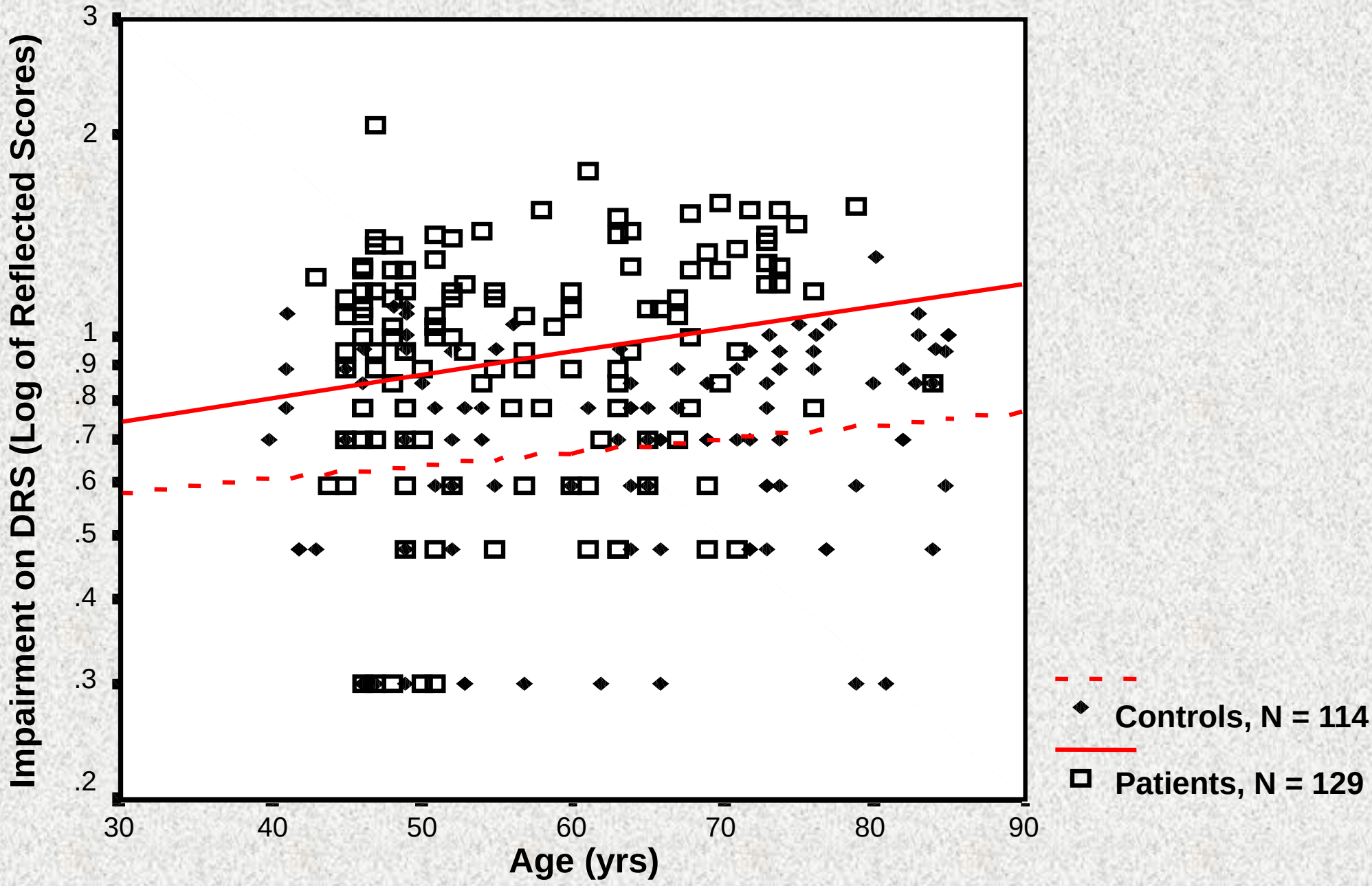
Jeste DV et al., ***Acta Psychiatrica Scandinavica,*** **107: 336-343, 2003;**

Folsom DP, et al., ***Schizophrenia Research,*** **108:207-13, 2009**

Correlations with Age in Schizophrenia Patients Aged 40-85 (N=192)

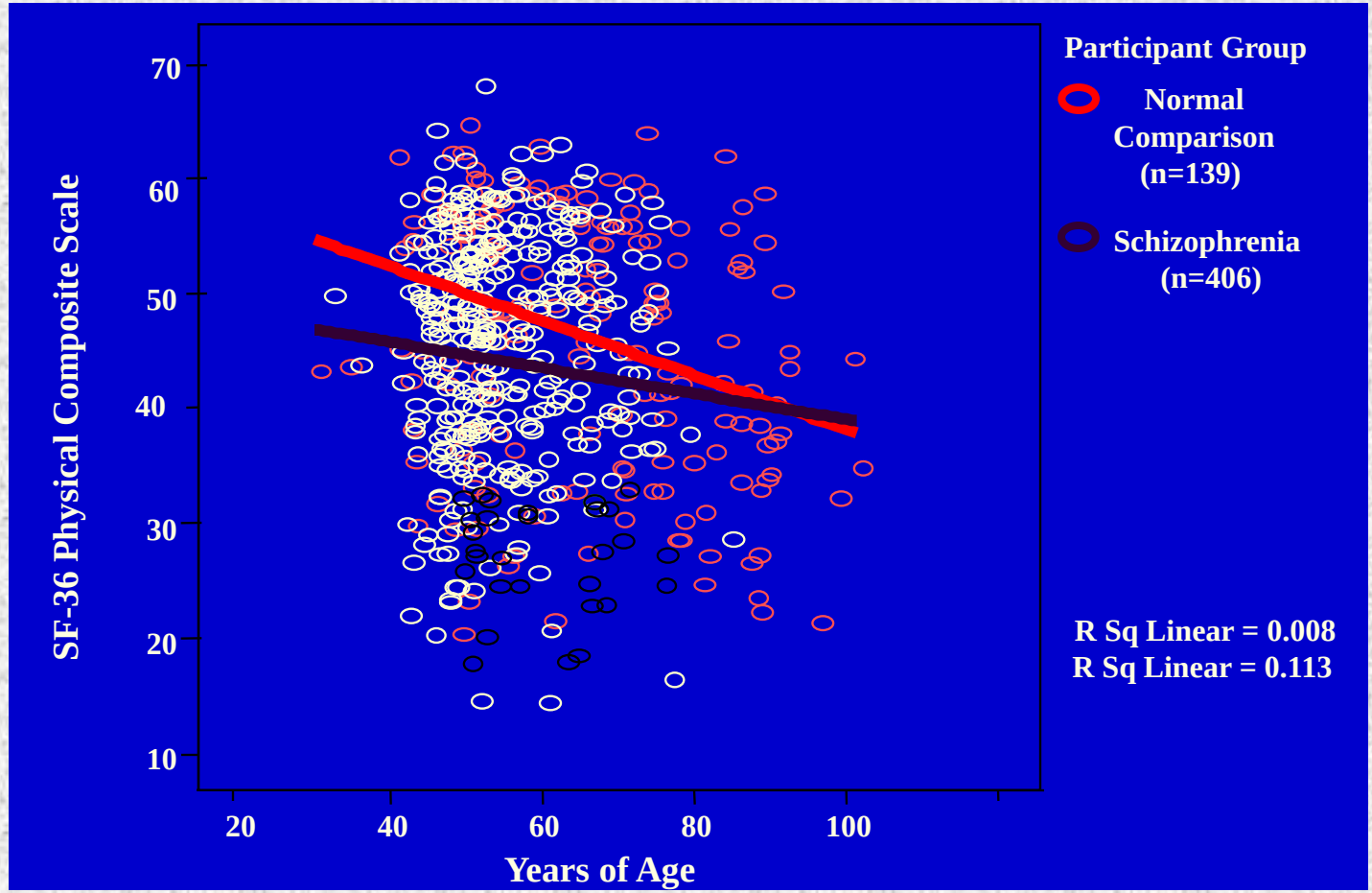
Positive Symptoms:	**SAPS**	**-0.19***
Negative Symptoms:	**SANS**	**-0.15**
Daily Neuroleptic Dose:		**-0.31****
Cognitive Impairment:	**DRS**	**0.21***

***p<0.05; **p<0.01**

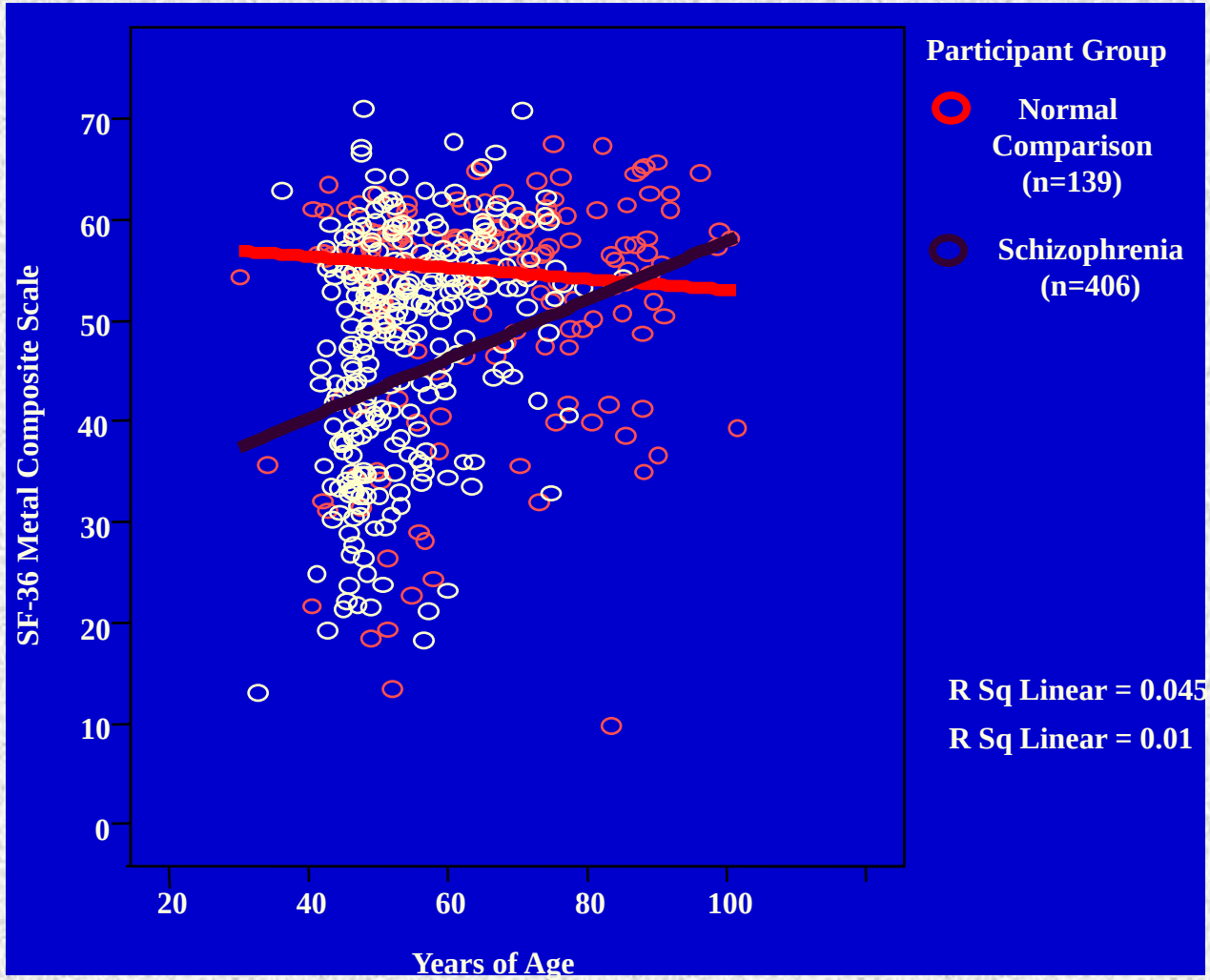


Eyler Zorrilla LT, et al., *Am J. Psychiatry,* 157: 1324-13262000

Age and SF-36 Physical Health Composite



Age and SF-36 Mental Health Composite



Remission of Schizophrenia: Earlier Studies

- Reported rates of remission or recovery range from 3% to 68%
- Variable use and definitions of terms: Cure, Recovery, Remission
- Bias in sample selection
- Inconsistent diagnostic criteria for schizophrenia
- Subjective evaluations

UCSD Criteria for Sustained Remission

- Met DSM-IV criteria for schizophrenia in past, but not currently;
- No hospitalization for last 5 years;
- Living independently; and
- Neuroleptic-free or on low dose of an antipsychotic

Auslander LA & Jeste DV, *Am J Psychiatry*, 161:1490-1493, 2004

Remission Study Conclusions

- 8% of the older schizophrenia patients living in the community met criteria for persistent symptomatic remission
- Remitted patients had somewhat impaired cognition & functioning suggesting that remission in schizophrenia may reflect a return to pre-morbid functioning rather than to “normal level”

Predictors of Sustained Remission from the Literature

- Social support
- Greater cognitive / personality reserve
- Early initiation of treatment
- NOT age or duration of illness

Late-Onset Schizophrenia: A Controversial Entity

Age of onset and diagnosis of schizophrenia in USA:

DSM-III (1980)
DSM-III-R (1987)
DSM-IV (1994)

European terminology:

Paranoia
Paraphrenia
Late paraphrenia

Questions

1. **Can schizophrenia manifest after age 45?**

   If it can,

2. **Why do these patients develop schizophrenia?**

   and

3. **What protects them from developing schizophrenia until late in life?**

Diagnosis

DSM-III-R or DSM-IV diagnosis with SCID

Age of onset of prodromal symptoms of schizophrenia

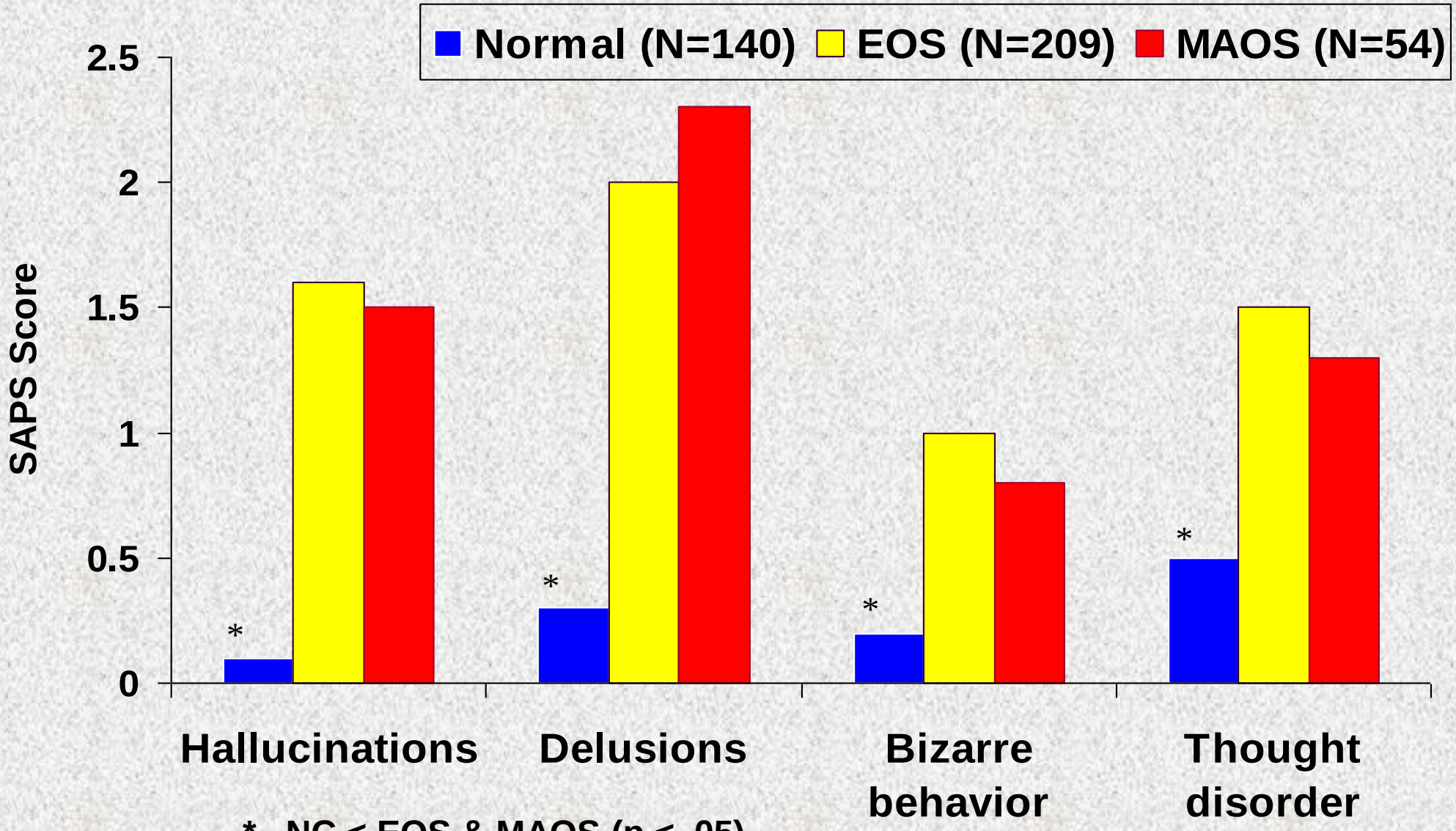
Specific inclusion and exclusion criteria

Diagnostic stability over follow-up period

Patient Characteristics

	Early-Onset Schizophrenia (EOS) (N=253)	Middle-Age Onset Schizophrenia (MAOS) (N=65)
Age of onset of schizophrenia	25 (7)	51 (8)
Duration of illness	31 (11)	10 (8)
Neuroleptic dose (mg CPZE/day)	250	126 *

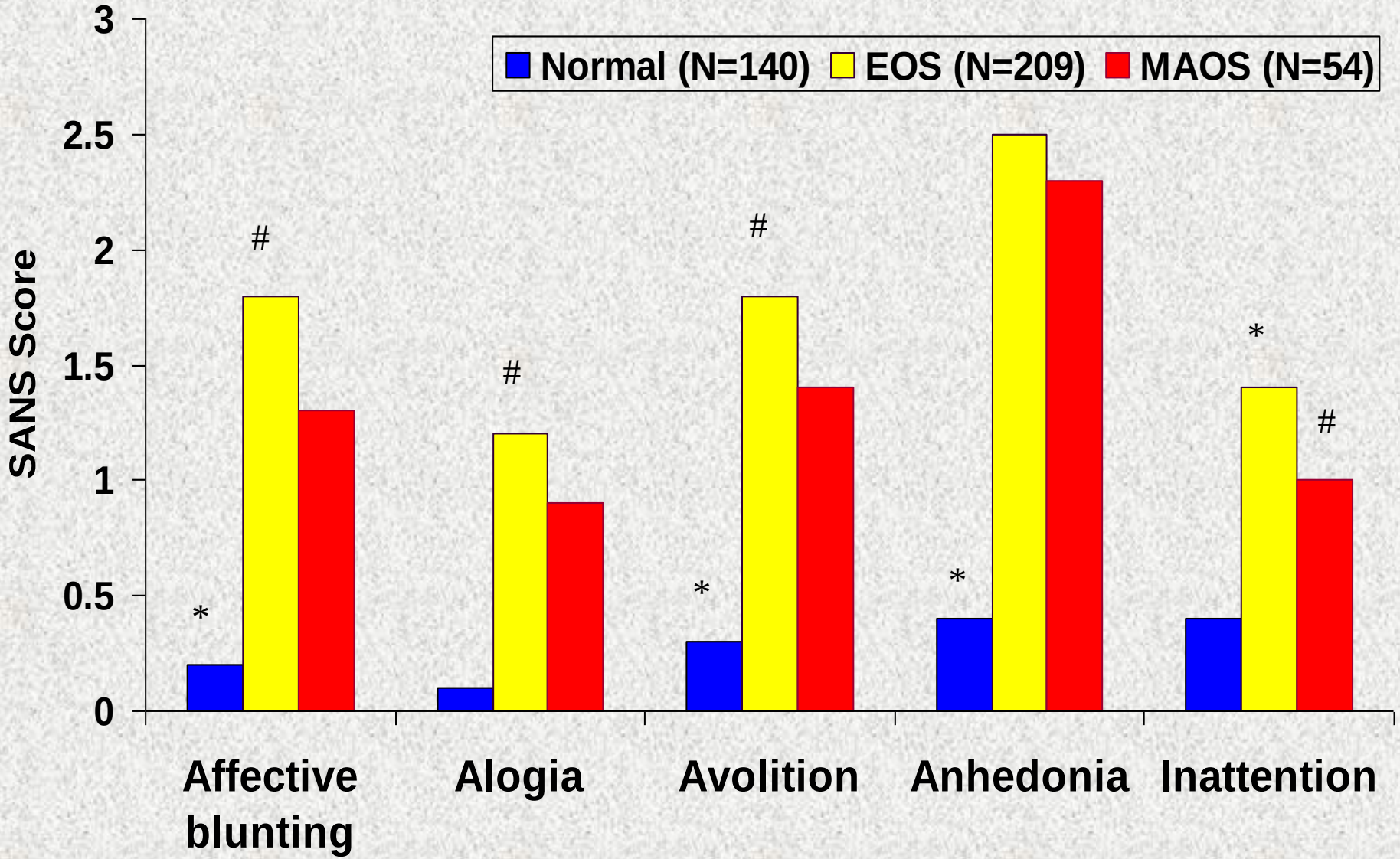
SAPS Subscale Scores



* NC < EOS & MAOS ($p < .05$)

Palmer BW, et al., *Harvard Review of Psychiatry*, 9:51-58, 2001

SANS Subscale Scores



* NC < EOS & MAOS ($p < .05$) # EOS > MAOS ($p < .05$)

Palmer BW, et al., *Harvard Review of Psychiatry*, 9:51-58, 2001

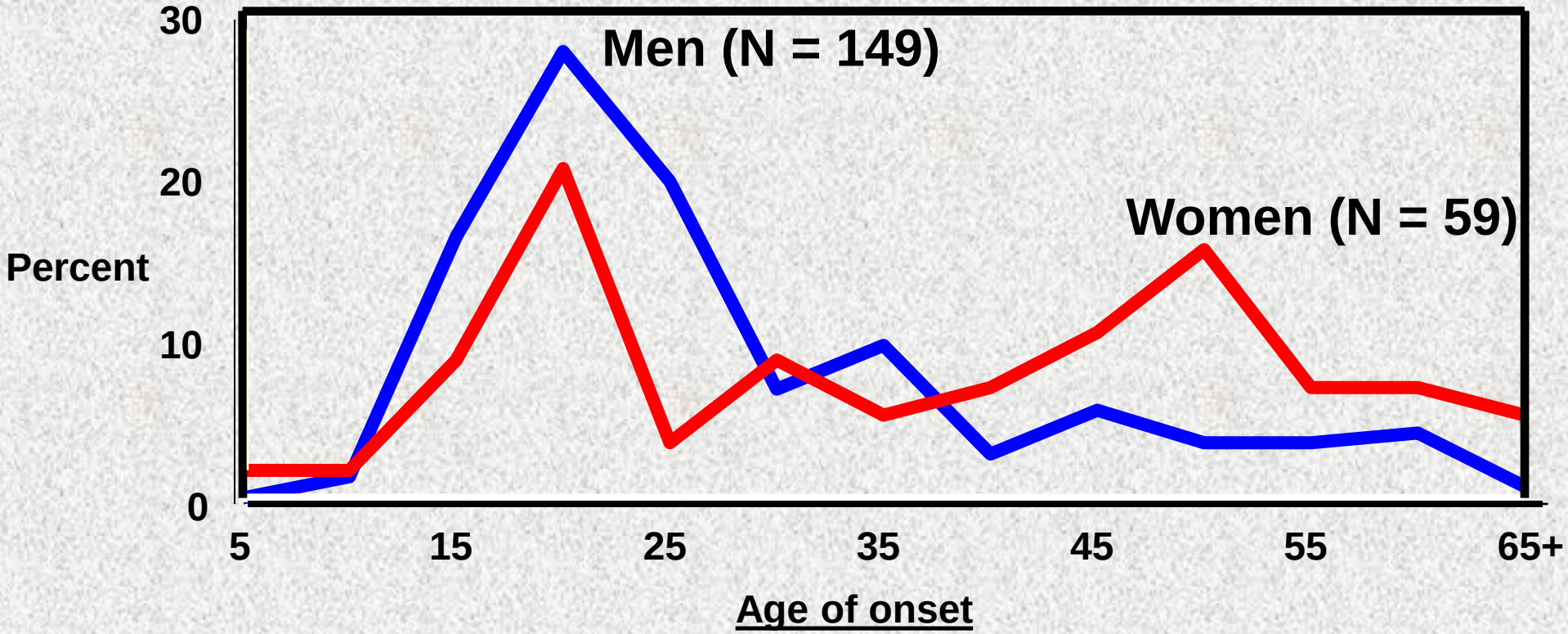
MAOS: Similarities with EOS

(I) Clinical

1) Severity of positive symptoms
2) Family history of schizophrenia
3) Minor physical anomalies
4) Childhood maladjustment
5) Sensory impairment

Jeste DV et al., *Am Psychiatry*, 152:722-730, 1995; *Am J Geriat Psychiatry*, 5:302-317, 1997

Age of Onset of Schizophrenia by Gender (Age > 45)



Kolmogorov-Smirnov pvalue < .0001

Lindamer et al., *Psychopharm. Bull.,* 33:221-228, 1997

MAOS: Differences from EOS

(I) Clinical

1) More common in women
2) Less severe negative symptoms
3) Mostly paranoid subtype
4) Greater % of patients ever married

Jeste DV et al., *Am Psychiatry*, 152:722-730, 1995; *Am J Geriatric Psychiatry*, 5:302-317, 1997

Psychosocial Factors

- **Premorbid Functioning: Suboptimal without being grossly psychopathological;**

  Premorbid personality may show paranoid or schizoid traits but not disorder.

- **Psychosocial Stressors: Retirement, bereavement, financial loss, physical disability, etc. may serve as precipitants and/or maintainers of psychosis.**

Neuropsychological Assessment

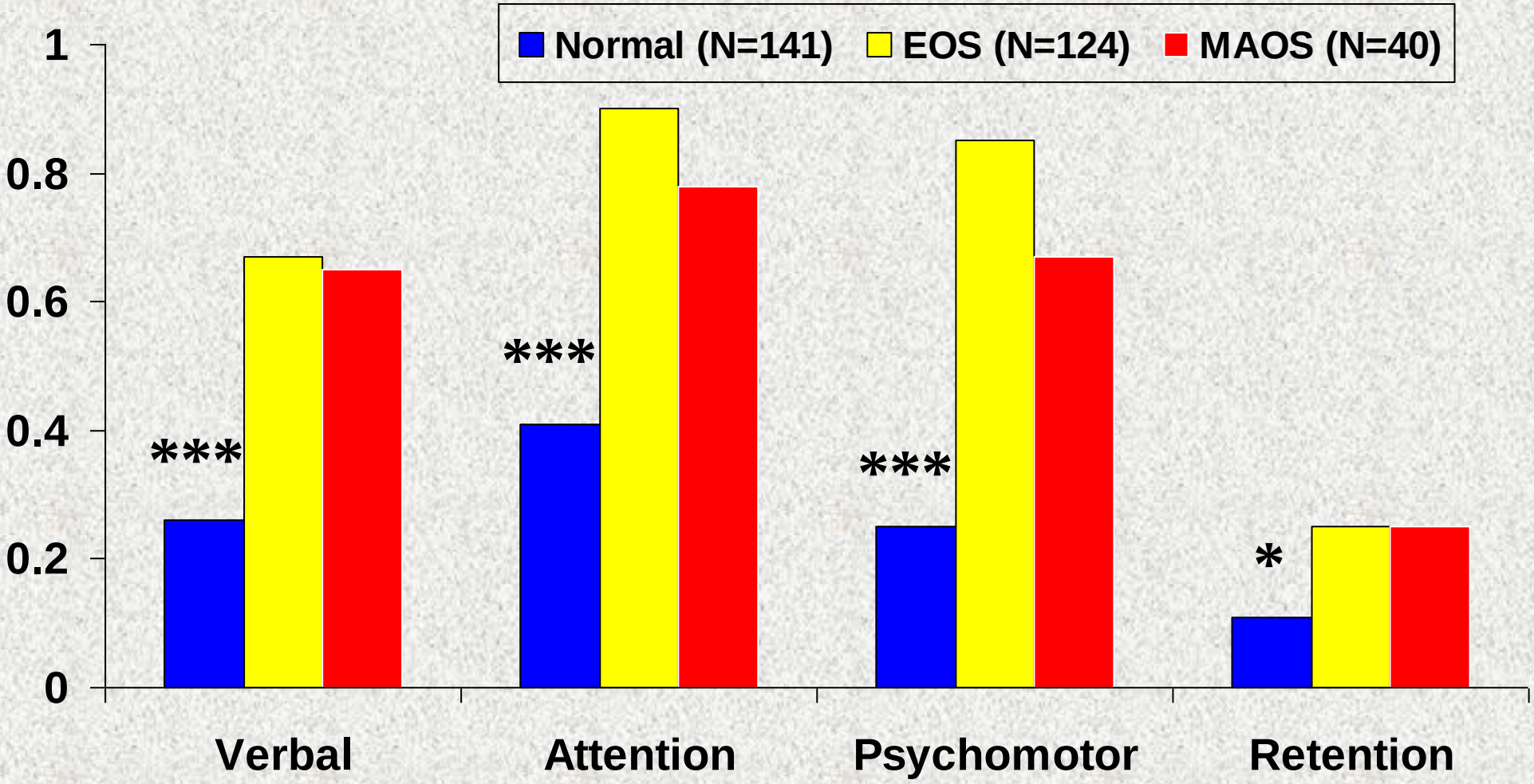
- **Expanded Halstead-Reitan battery, Age-, gender-, and education-corrected, T-, and deficit-scores for 7 ability areas:**

1) Verbal, 2) Attention, 3) Psychomotor,

4) Memory (retention), 5) Learning,

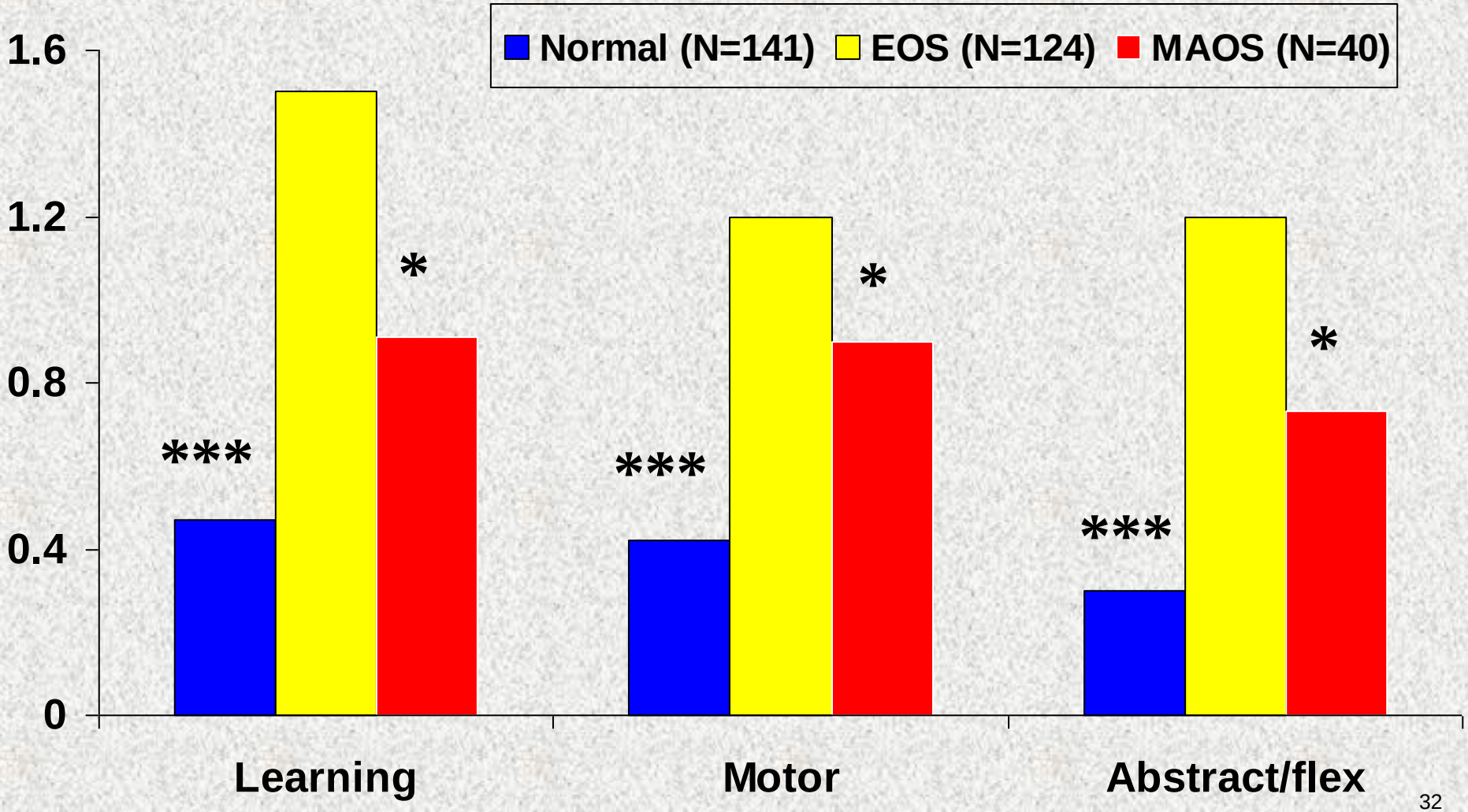
6) Motor, and 7) Abstraction.

Neuropsychological Deficit Scores



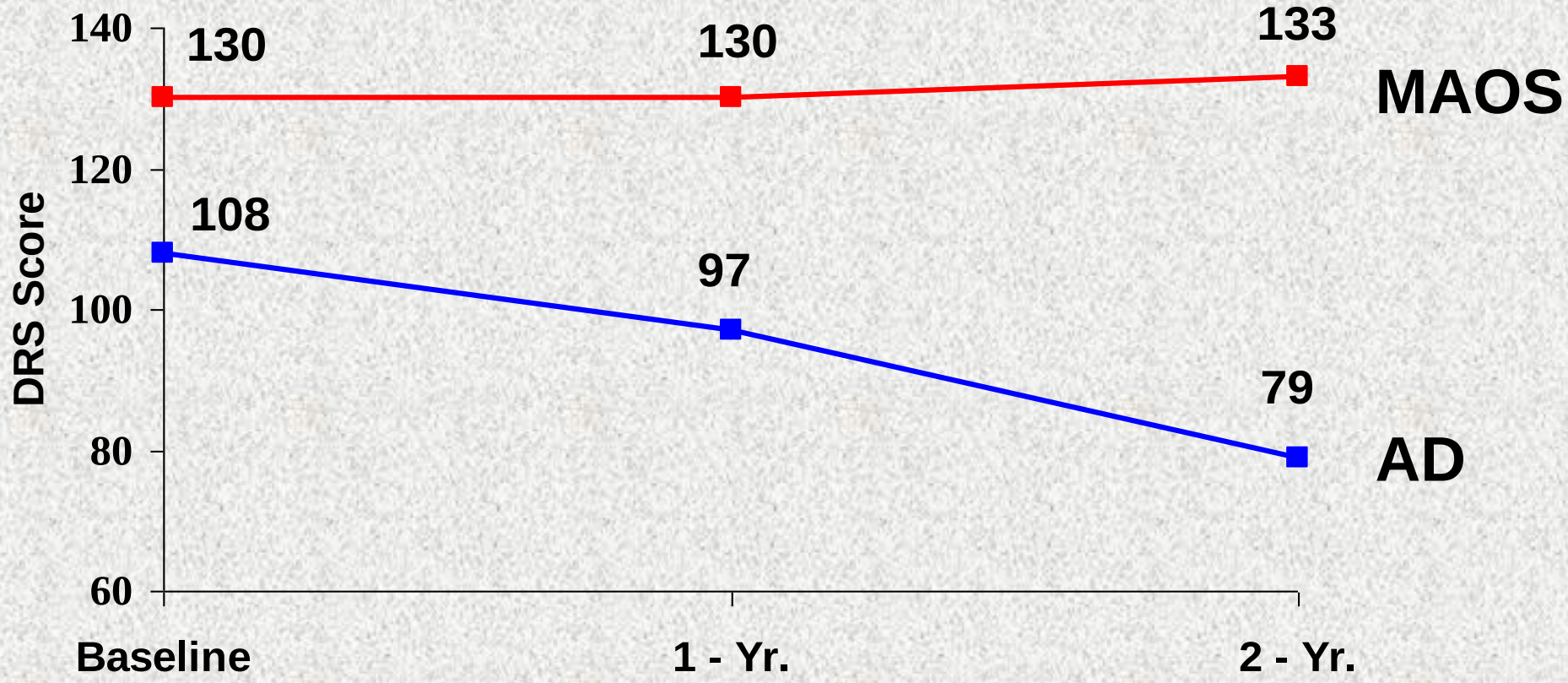
* p < .05; *** p < .0001(NC < MAOS, EOS)

Neuropsychological Deficit Scores



* p .05; *** p<.0001 (NC < MAOS < EOS)

MAOS (N=29) vs. Alzheimer Disease (N=61): Longitudinal Study of Mattis' Dementia Rating Scale (DRS)



MAOS: Similarities with EOS

(II) Neuropsychological

(1) Overall pattern of cognitive impairment

(III) MRI

(1) Nonspecific MRI abnormalities

(IV) Course & Treatment

(1) Chronic Course

(2) Qualitative response to neuroleptics

(3) Increased mortality

Jeste DV et al., *Am Psychiatry*, 152:722-730, 1995; *Am J Geriatric Psychiatry*, 5:302-317, 1997

MAOS: Differences from EOS

(II) Neuropsychological

(1) Less severe impairment in learning and in abstraction

(III) Course & Treatment

(1) Need for lower doses of neuroleptics

Jeste DV et al., *Am Psychiatry*, 152:722-730, 1995; *Am J Geriat Psychiatry*, 5:302-317, 1997

Very Late-Onset Schizophrenia-like Psychosis

Heterogeneous group of disorders:

- **Psychosis of dementia**
- **Psychosis secondary to general medical conditions or substance use**
- **Mood disorder with psychotic features**
- **Delusional disorder**
- **Psychosis NOS**

Howard R et al., *Am J Psychiatry*, 157:172-178, 2000

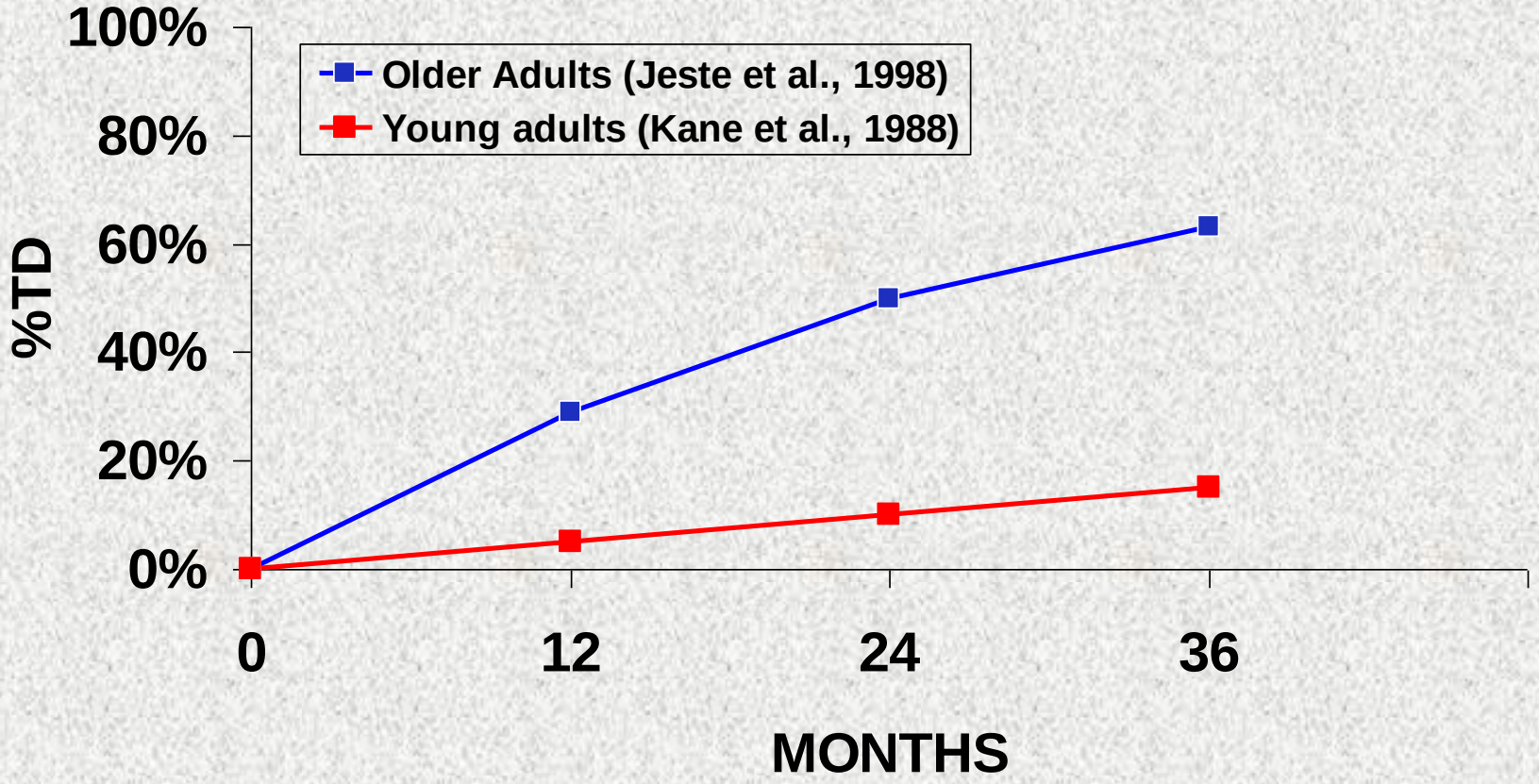
International Consensus Statement on Late-Onset Schizophrenia

In terms of epidemiology, symptomatology, and identified pathophysiology, LOS (onset after age 40) and very late-onset schizophrenia-like psychosis (onset after age 60) have face validity and clinical utility.

-Howard, Rabins, Seeman, Jeste, and International LOS Group (representatives from Australia, Brazil, Canada, Denmark, France, India, Japan, Spain, Switzerland, UK and USA)

Howard R et al., *Am J Psychiatry*, 157:172-178, 2000

Cumulative Incidence of TD with Conventional Antipsychotics



Kane J et al., *J Clin Psychopharm*, 1988; Jeste DV et al., *Am J Geriatric Psychiatry*, 7:70-76, 1998

Risperidone vs Olanzapine in Elderly Schizophrenia Pts.

- International, double-blind, 8-week RCT*
- 176 patients, aged >60 years
- Schizophrenia or schizoaffective disorder
- Randomly assigned to flexible doses of Risperidone (1-3; median 2 mg/d) or Olanzapine (5-20; median 10 mg/d)

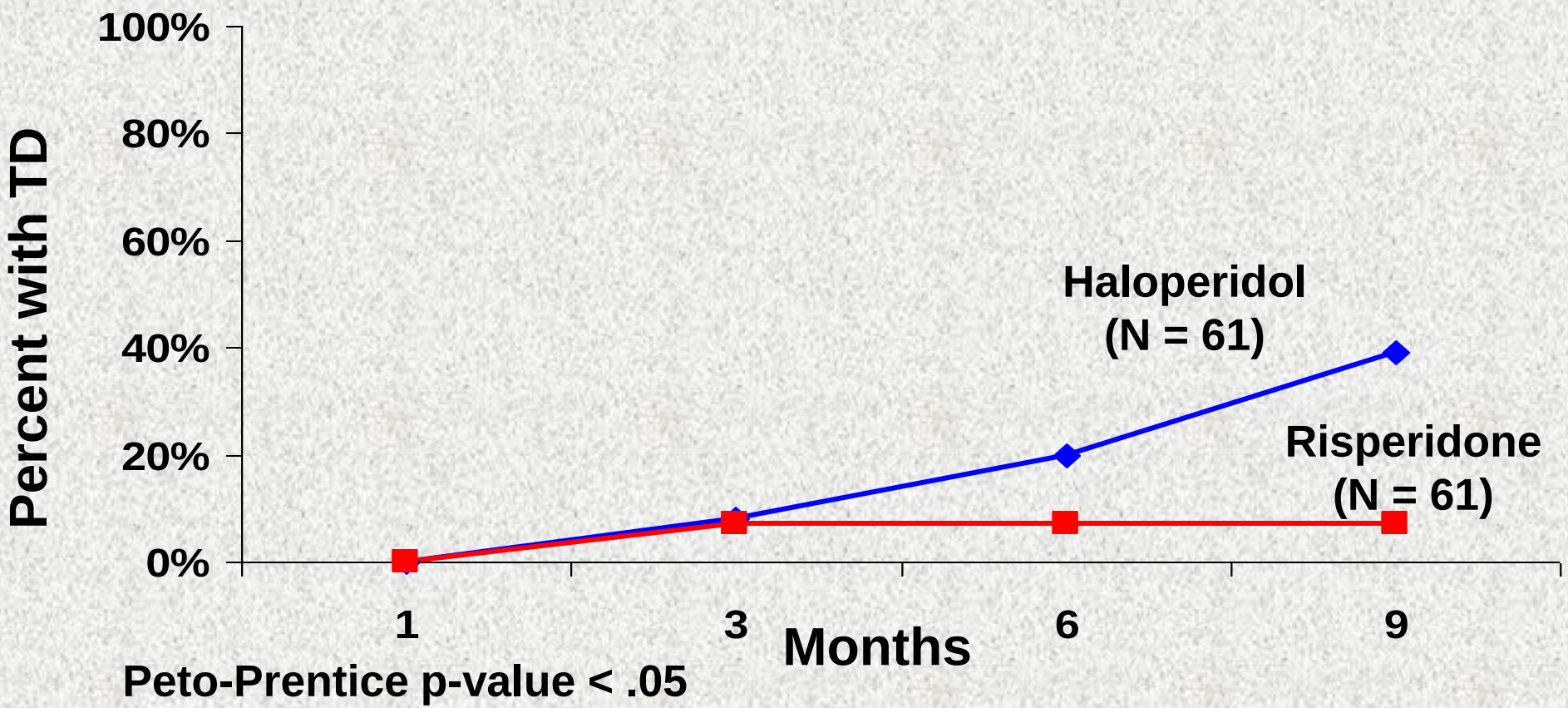
Jeste DV, et al., *American Journal of Geriatric Psychiatry*, 11:638-647, 2003

Risperidone Vs. Olanzapine

- Both atypical antipsychotics produced significant improvement from baseline scores on PANSS
- No significant difference between the 2 drugs on Psychopathology, Cognitive function, QTc, or Reports of EPS or anticholinergic side effects
- Greater weight gain with olanzapine (p=.05)

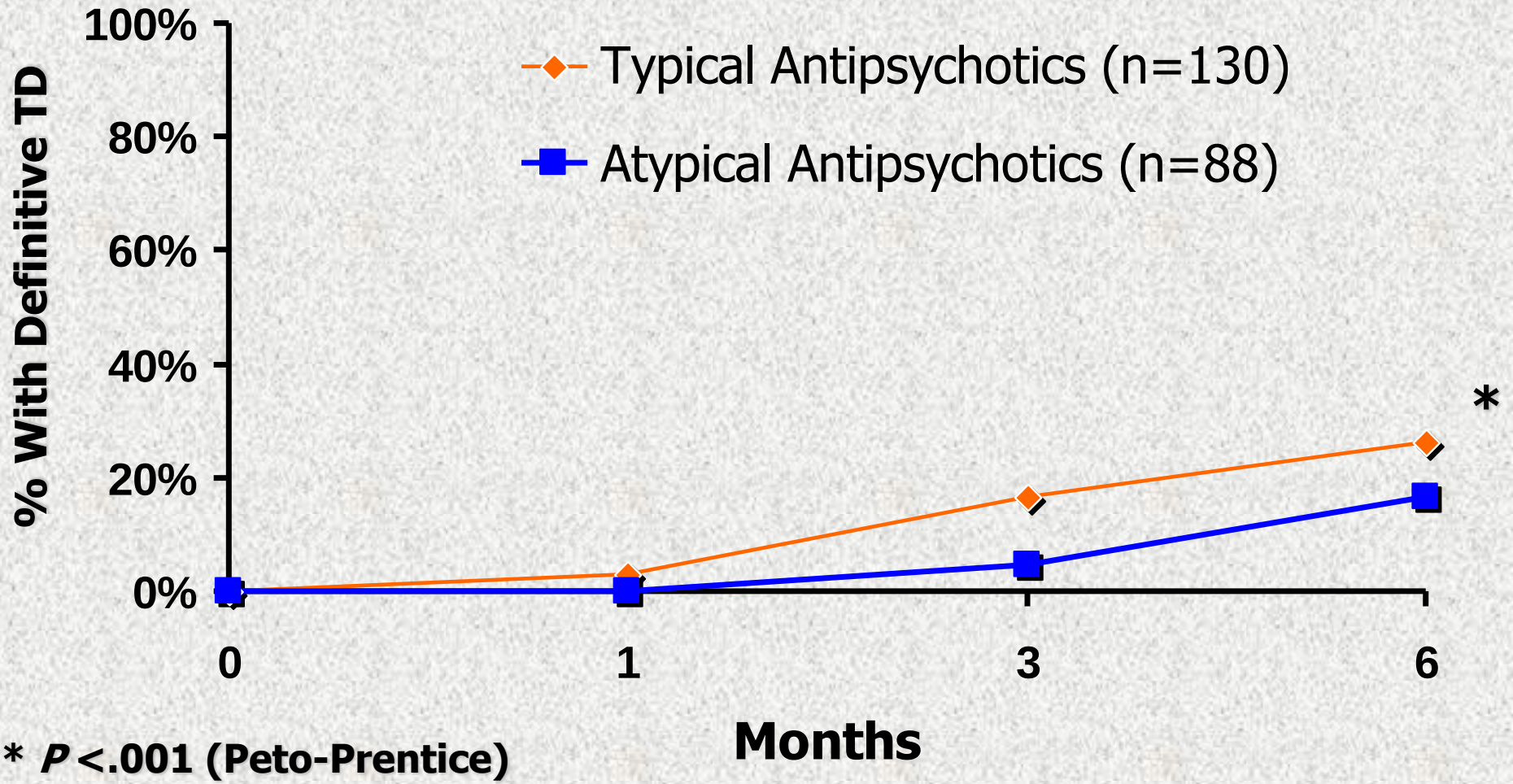
Jeste DV, et al., *American Journal of Geriatric Psychiatry*, 11:638-647, 2003

TD Incidence in Older Patients: Haloperidol versus Risperidone (1mg/d)



Jeste et al., *JAGS,* 47: 716-719, 1999

Cumulative Incidence of Definitive TD in Older Patients With Borderline Dyskinesia



* *P* <.001 (Peto-Prentice)

Dolder C & Jeste DV. *Biol Psychiatry*. 2003, 53:1142-45

Atypical Antipsychotics: Possible Long-Term Side Effects

- Weight gain
- Type 2 diabetes mellitus
- Hyperlipidemia
- Hyperprolactinemia
- Cardiac conduction disorders
- Strokes (in dementia patients)
- Increased mortality (in dementia patients)

FDA Warnings About Antipsychotic Use

- In all age groups: Weight gain, Diabetes, Hyperlipidemia
- In dementia patients: Strokes, and Mortality

FDA Black-Box Warning Re. Strokes with Atypical Antipsychotics in Dementia Pts.

- A double-blind placebo-controlled trial of risperidone in elderly patients with dementia indicated a higher risk of strokes with risperidone compared to placebo.[1]
- The FDA analyzed data from all the placebo-controlled trials in dementia patients, & found a significantly higher risk of strokes with several atypical antipsychotics than with placebo
- This led to black-box warnings re. increased risk of strokes with risperidone, olanzapine, & aripiprazole in dementia patients

1. Brodaty et al., 2003

FDA Black Box Warning Re. Mortality with Antipsychotic Use in Elderly Dementia Patients

- 17 Placebo-controlled trials of atypical antipsychotics in dementia patients with behavioral disorders
- Mortality with atypical antipsychotics 1.6 to 1.7 times greater than with placebo
- Common causes were cardiac (heart failure) or infectious (pneumonia)
- June 2008: Warning extended to conventional neuroleptics

Recommended Dosages in Older Patients with Schizophrenia (mg/day)

Drug	Initial	Typical Range
Clozapine	6.25-12.5	50-150
Risperidone	0.25-0.5	1-3
Olanzapine	2.5-5	5-15
Quetiapine	12.5-25	75-200

Other Atypical Antipsychotics

- Ziprasidone
- Aripiprazole
- Others

Psychosocial Tx of Late-Life Schizophrenia

- **Cognitive Behavior Social Skills Training**
- **Functional Adaptation Skills Training**
- **Medication Adherence Therapy**
- **Vocational Rehabilitation**
- **PEDAL (**Programa de Entrenamiento para el Desarrollo de Aptitudes para Latinos) **for older Latino patients**[1]

1. Patterson TL, Bucardo J, McKibbin CL, *et al*. Schizophr Bull 2005; 31:922-930.

Cognitive Behavioral, Social Skills Training (CBSST)

- Three modules, each with 4 weekly sessions, to be repeated, for a total of 24 group sessions
  - CBT – Thought challenging
  - SST – Asking for support
  - CBSST – Solving problems
- Manualized treatment, with homework assignment after "classes"

Granholm E, et al., American Jr. of Psychiatry, 162:520-529, 2005

Randomized Controlled Trial of CBSST

- 76 Patients with schizophrenia or schizoaffective disorder randomized to CBSST or Tx as usual
- Blind assessments on Independent Living Skills Survey, Beck's Cognitive Insight Scale, Comprehensive Module Test for CBSST skills, and Psychopathology (PANSS, HAM-D) at baseline, 3 months, & 6 months

Granholm E, et al., American Jr. of Psychiatry, 162:520-529, 2005

CBSST Outcomes

- 86% Patients stayed in treatment
- No significant change in medication management
- Significant improvement at 3 & 6 months on:
  - Mastery of CBSST skills
  - Frequency of social activities
  - Cognitive insight
  - But not on psychopathology

Granholm E, et al., American Journal of Psychiatry, 162:520-529, 2005

Functional Adaptation Skills Training (FAST)

- Teaching skills for: Communication, Transportation, Medication management, Social skills, Organization & planning,

  Financial management
- 24 semi-weekly 2-hour group sessions
- FAST-treated patients showed significantly better everyday functioning than controls at end of treatment and 3 months later

Patterson T, et al., Schizophrenia Research 86:291-299, 2006

Treatment - Summary

- Atypical antipsychotics have a considerably lower risk of EPS and TD than conventional neuroleptics, but they have other major adverse effects such as metabolic disorders
- Medications should be used, only when needed, in lowest effective doses and for shortest period necessary, and should be supplemented by psychosocial therapies

Suggested Readings

- Jeste DV, Symonds LL, Harris MJ, et al.: Non-dementia non-praecox dementia praecox?: Late-onset schizophrenia. Am J Geriat Psychiatry 5:302-317, 1997
- Howard R, Rabins P, Seeman MV, et al.: Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. Am J Psychiatry,157:172-178, 2000
- Jeste DV, Twamley EW, Eyler Zorrilla LT, et al.: Aging and outcome in schizophrenia. Acta Psychiatr Scandi 107: 336-343, 2003

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- Auslander LA and Jeste DV: Sustained remission of schizophrenia among community-dwelling older outpatients. Am J Psychiatry 161:1490-1493, 2004
- Patterson TL, McKibbin C, Mausbach BT, et al.: Functional Adaptation Skills Training (FAST): A randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. Schiz Res 86:291-299, 2006
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Which of the following is true regarding treatment of late-onset schizophrenia?

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Which of the following are long-term adverse effects of atypical antipsychotics?

A. Weight gain
B. Type 2 diabetes mellitus
C. Dyslipidemia
D. Increase in strokes and mortality in dementia patients
E. Any of the above

Answers to Self-Assessment Questions

1) E
2) B
3) D
4) C
4) E