

# **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

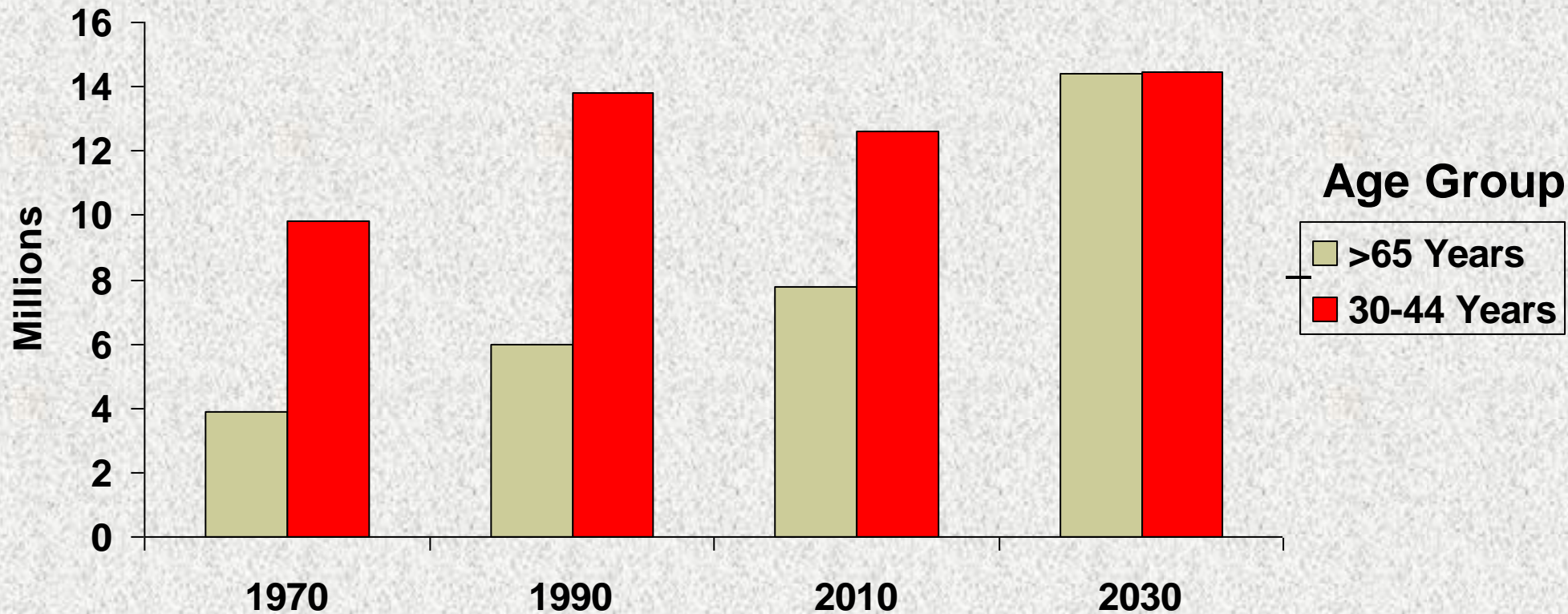
- Schizophrenia can manifest for the first time after age 40
- Course of schizophrenia in late life is generally characterized by persistence of negative symptoms, absence of rapid cognitive decline, and modest improvement in positive symptoms
- Very late-onset schizophrenia-like psychosis (with onset 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



# Late-Life Course of Schizophrenia

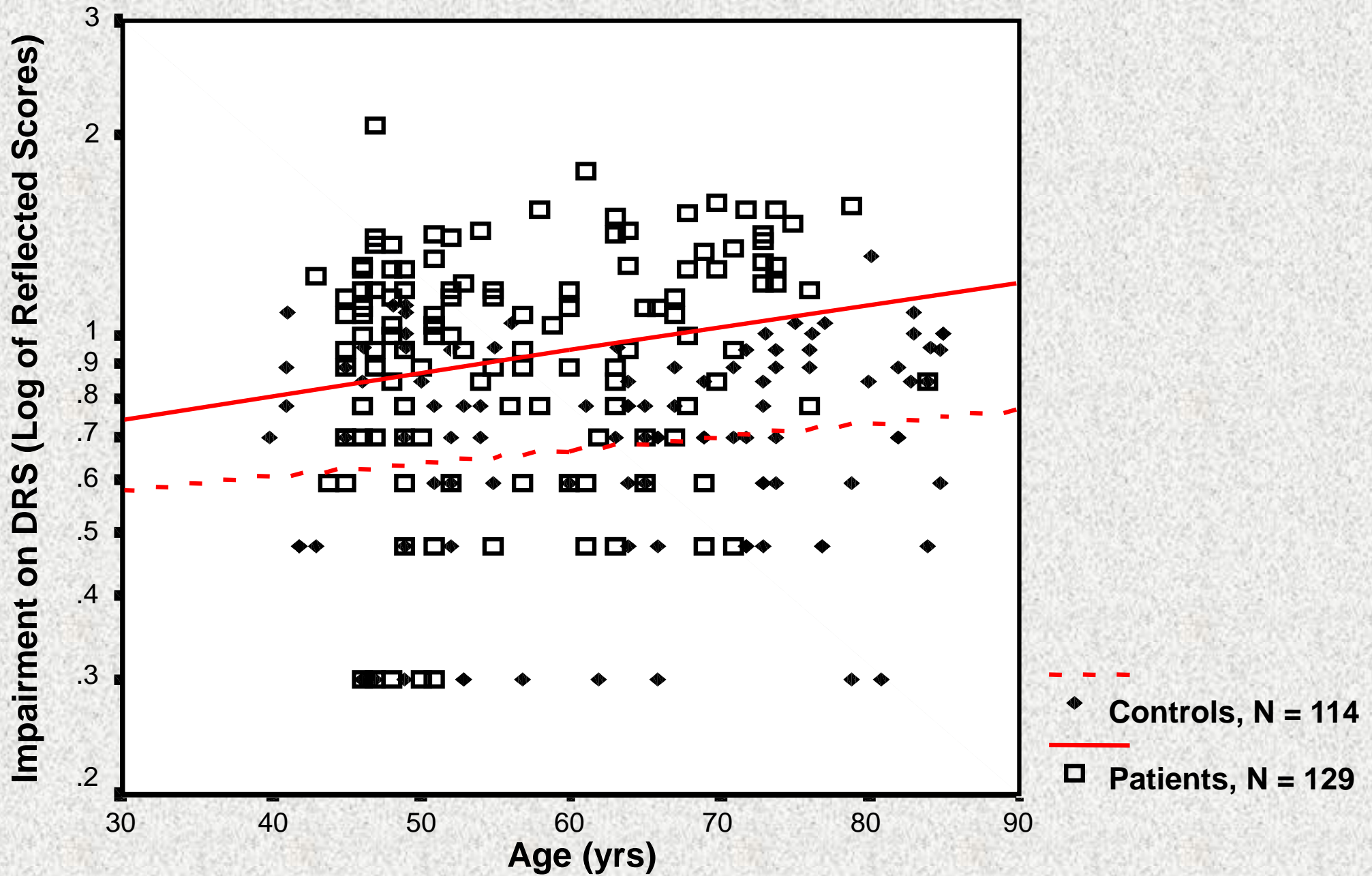
- Over 1,200 middle-aged and older people with schizophrenia studied at UCSD since 1987
- Relatively stable and non-deteriorating course
- Improvement in Tx adherence and in psychotic symptoms, with fewer relapses, with aging
- Rate of age-related cognitive change is similar in patients and normal subjects
- 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)

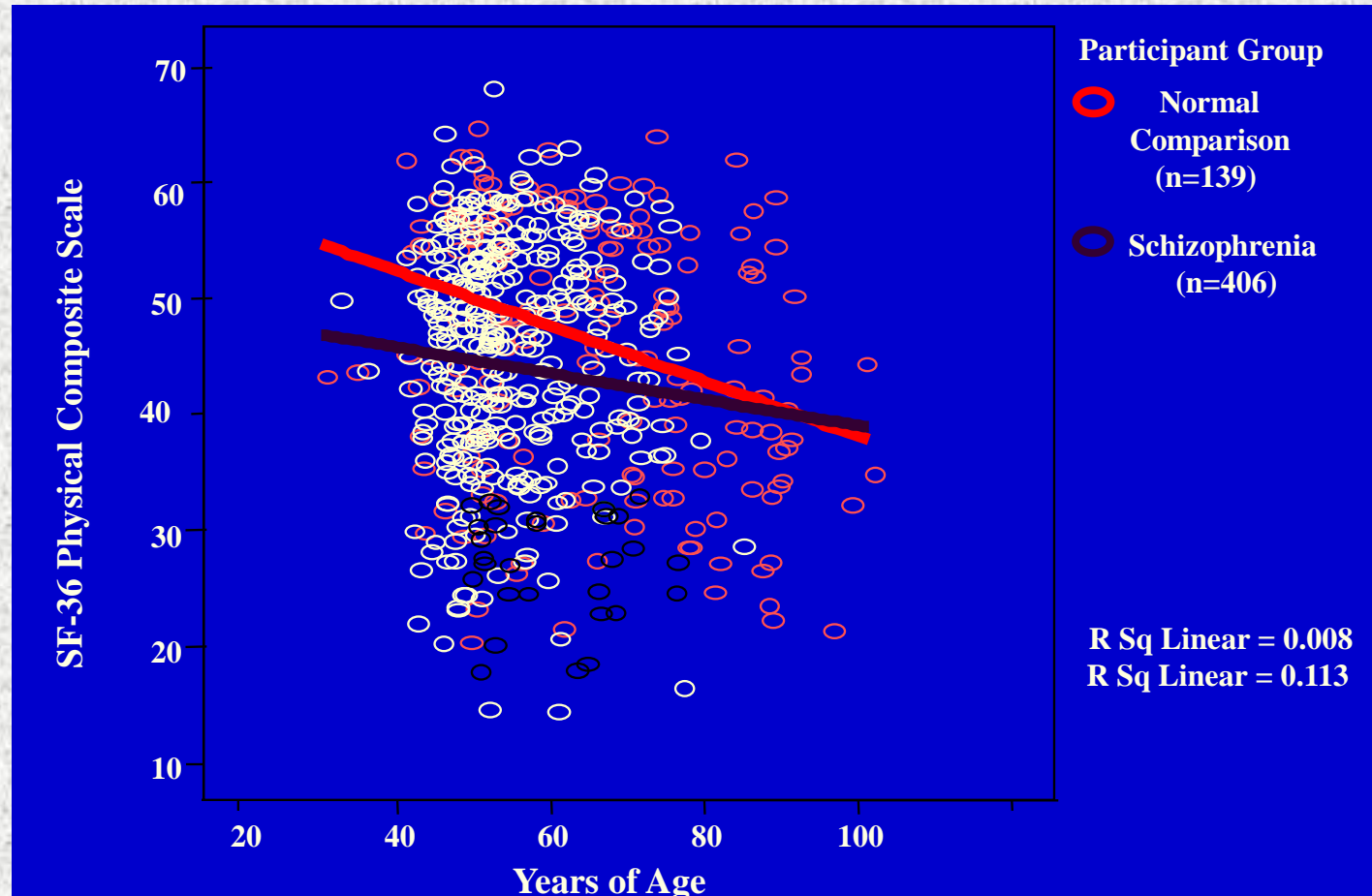
<b>Positive Symptoms:</b>	<b>SAPS</b>	<b>-0.19*</b>
<b>Negative Symptoms:</b>	<b>SANS</b>	<b>-0.15</b>
<b>Daily Neuroleptic Dose:</b>		<b>-0.31**</b>
<b>Cognitive Impairment:</b>	<b>DRS</b>	<b>0.21*</b>

**\*p<0.05;    \*\*p<0.01**



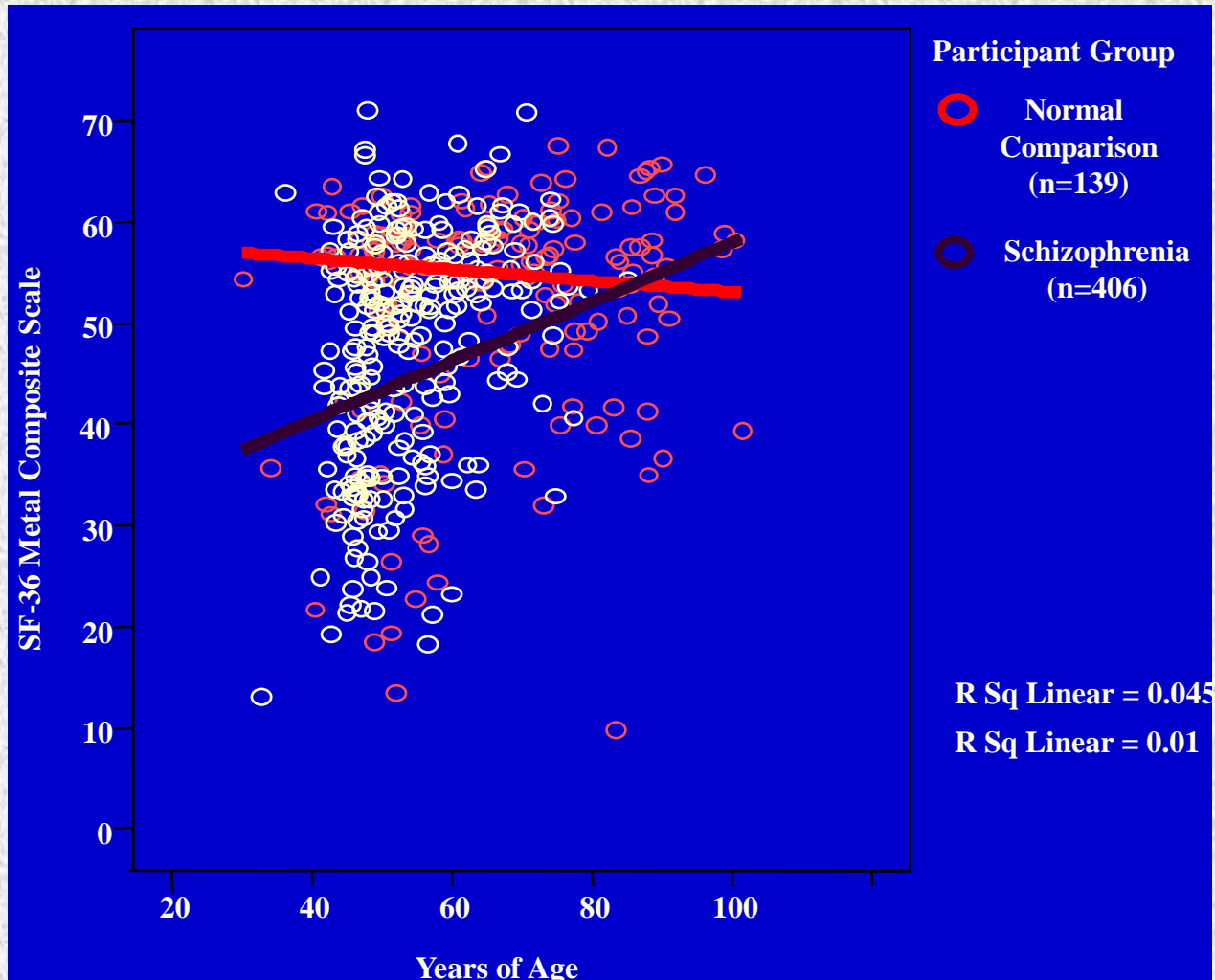
# Age and SF-36

## 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**

# 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**

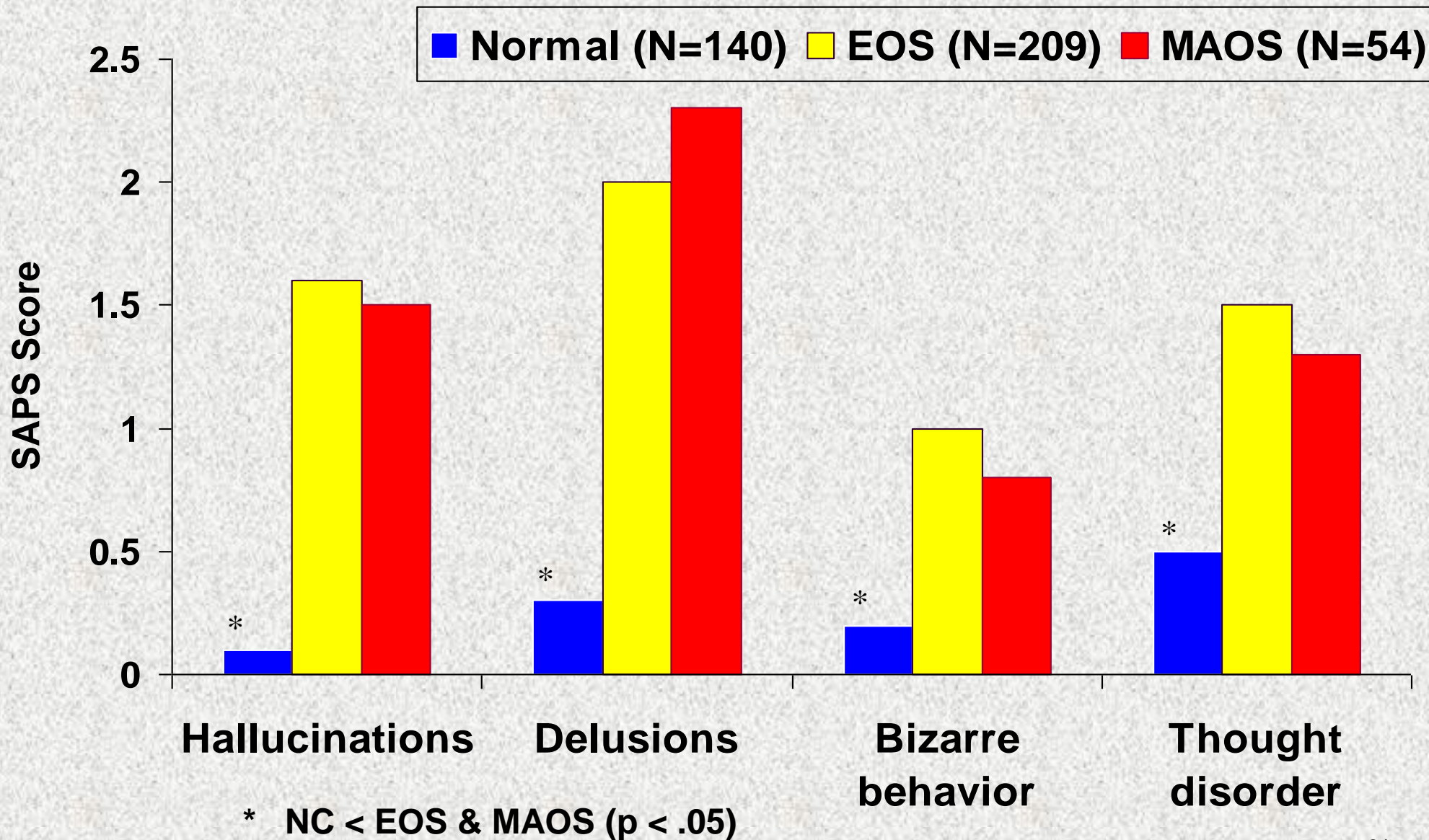
**Specific inclusion and exclusion criteria**

**Diagnostic stability over follow-up period**

# Patient Characteristics

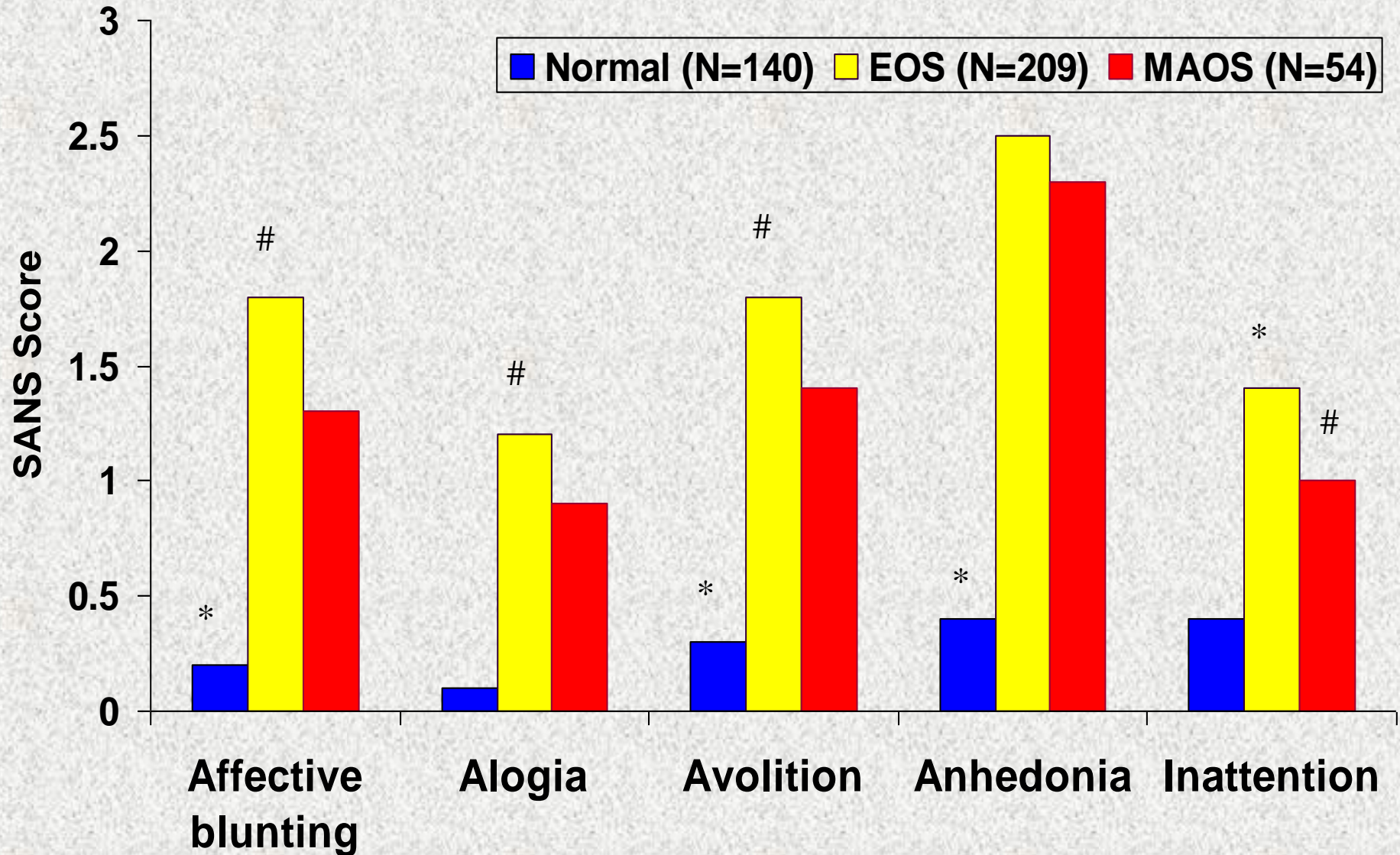
	<b>Early-Onset Schizophrenia (EOS) (N=253)</b>	<b>Middle-Age Onset Schizophrenia (MAOS) (N=65)</b>
<b>Age of onset of schizophrenia</b>	<b>25 (7)</b>	<b>51 (8)</b>
<b>Duration of illness</b>	<b>31 (11)</b>	<b>10 (8)</b>
<b>Neuroleptic dose (mg CPZE/day)</b>	<b>250</b>	<b>126 *</b>

# SAPS Subscale Scores





# SANS Subscale Scores



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

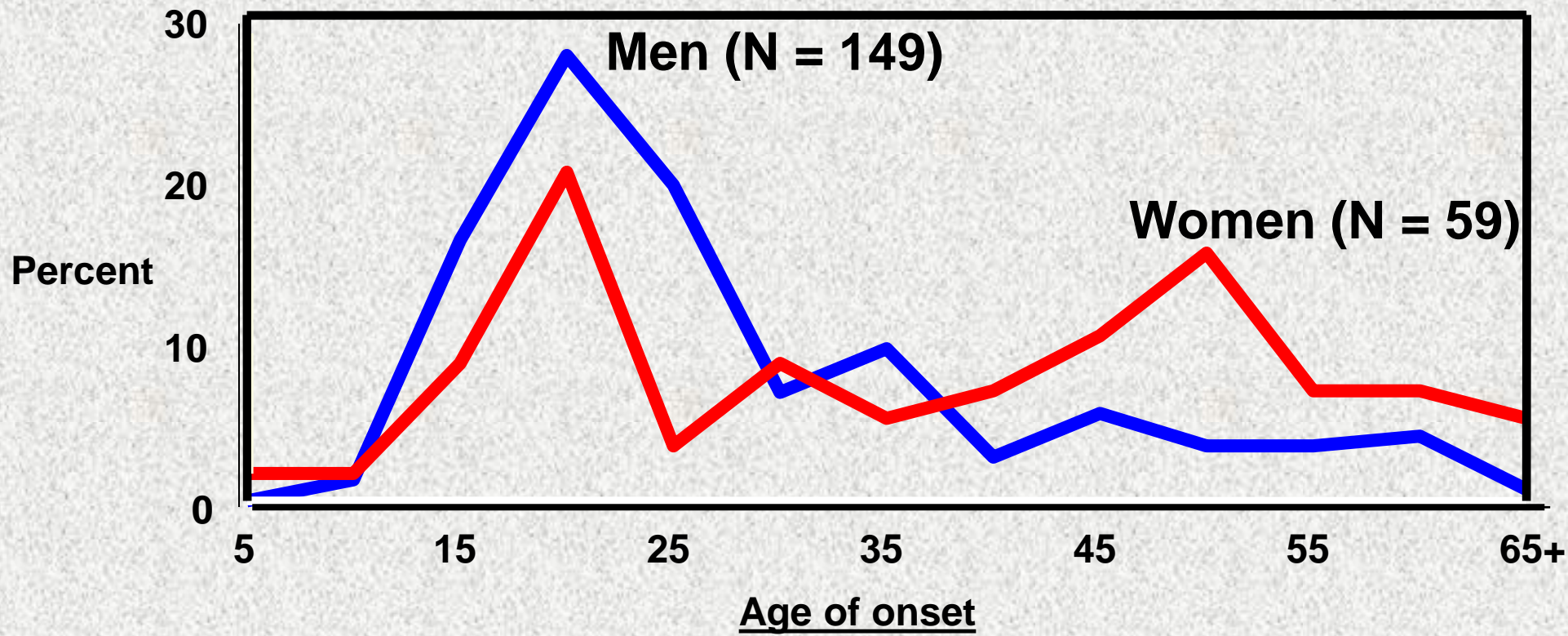
# **MAOS: Similarities with EOS**

## **(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)**

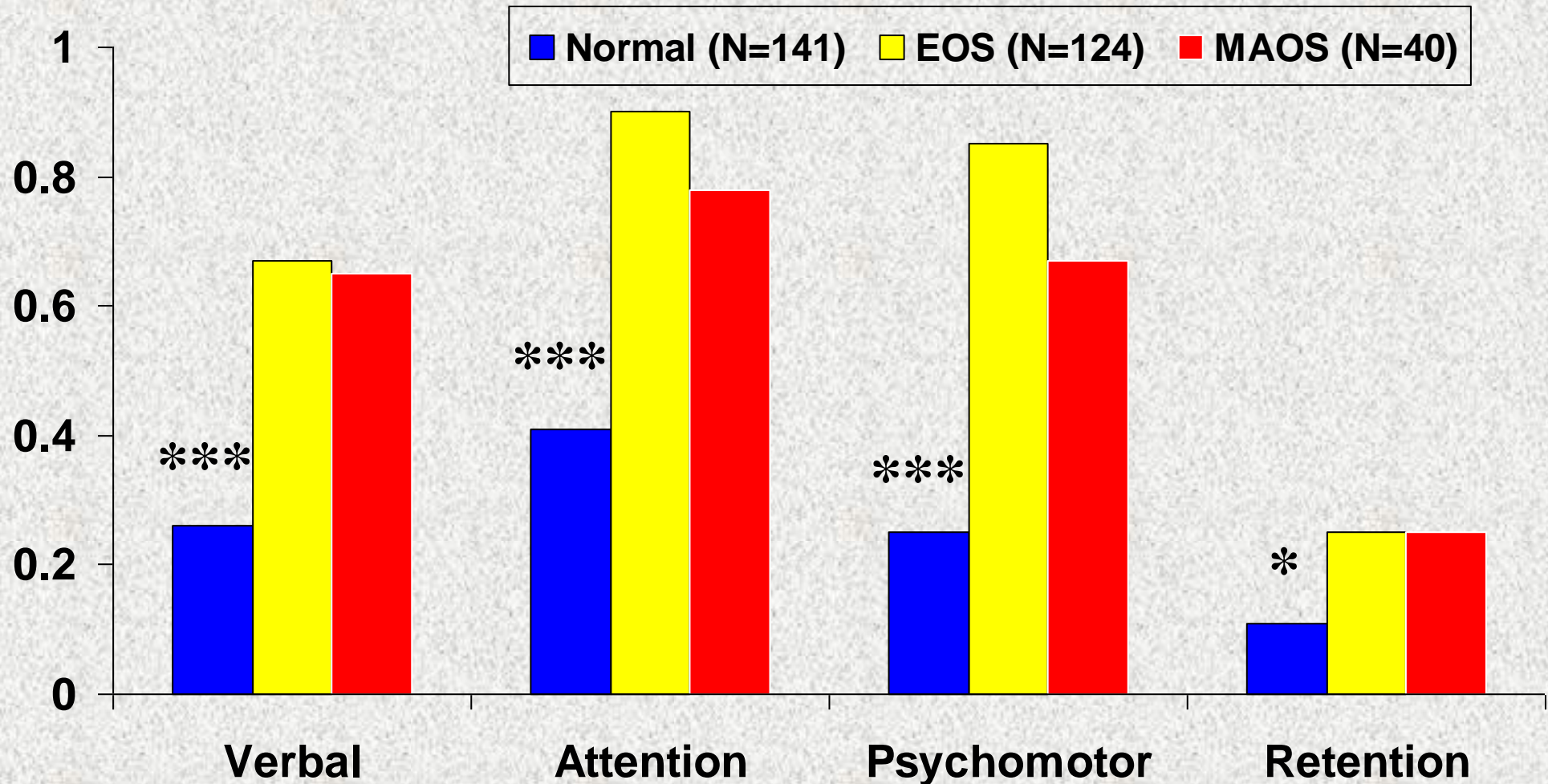
# **Psychosocial Factors**

- ❖ **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**

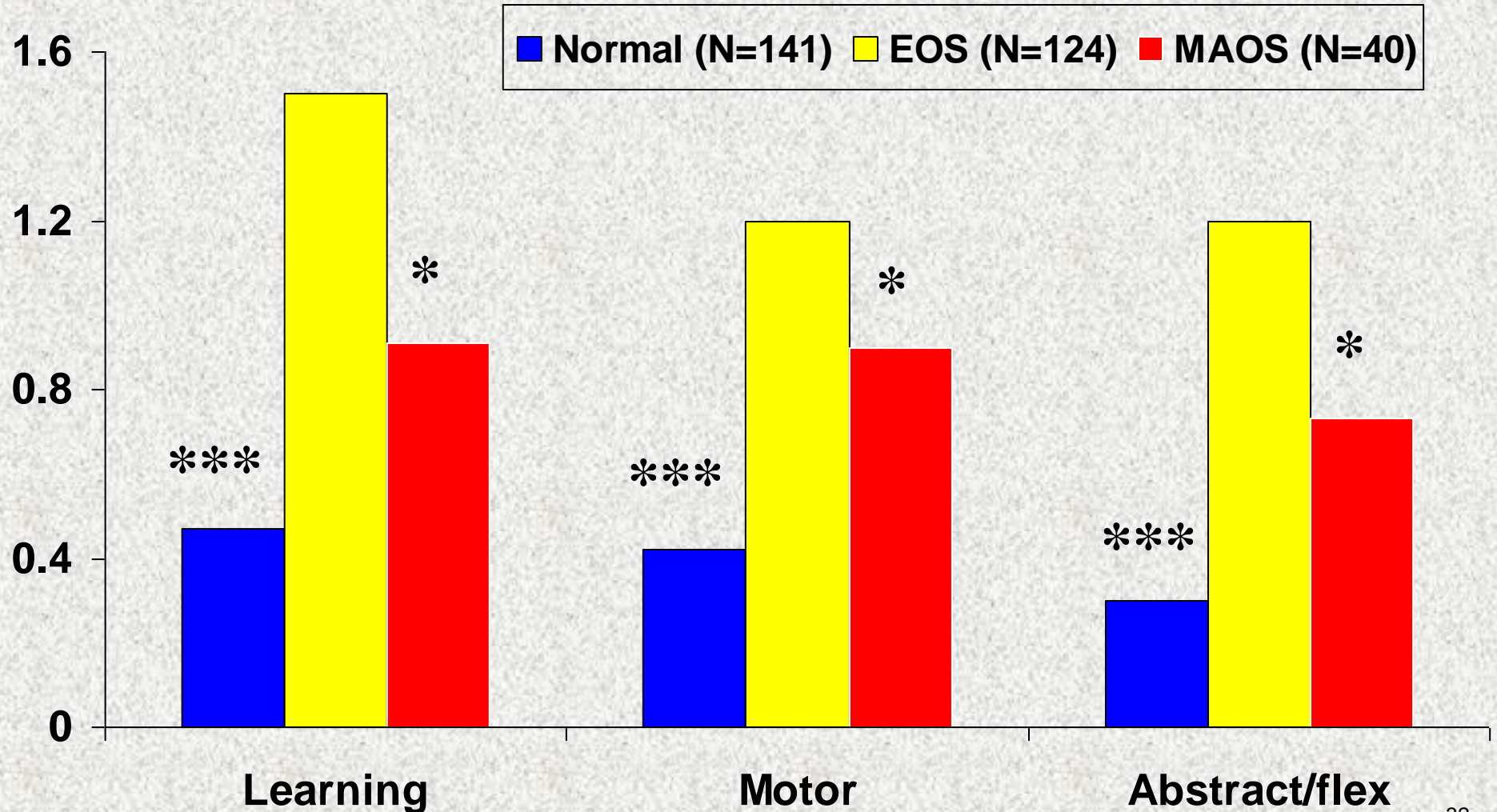
- ❖ **Expanded Halstead-Reitan battery, Age-, gender-, and education-corrected, T-, and deficit-scores for 7 ability areas:**
  - 1) Verbal, 2) Attention, 3) Psychomotor,**
  - 4) Memory (retention), 5) Learning,**
  - 6) Motor, and 7) Abstraction.**

# Neuropsychological Deficit Scores



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

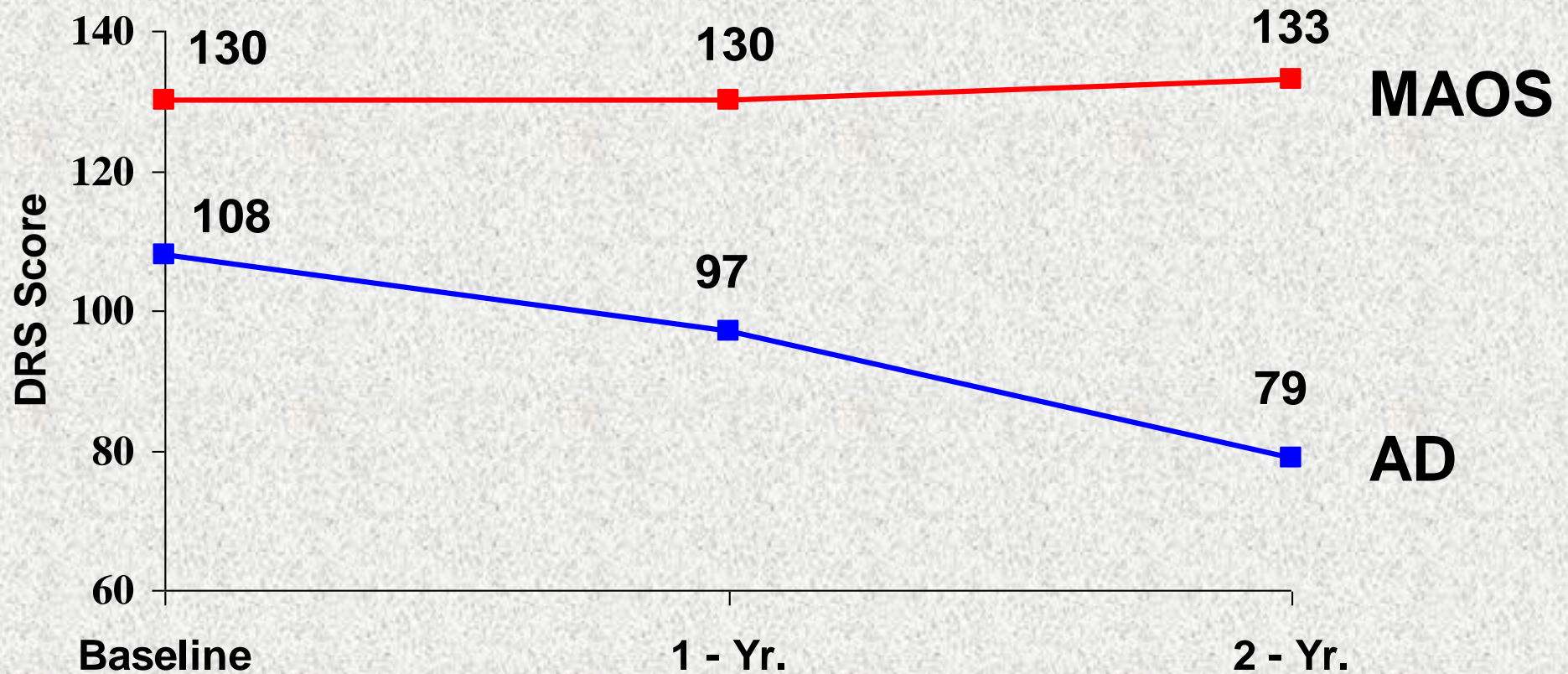
# Neuropsychological Deficit Scores



\* 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**

# **Very Late-Onset** **Schizophrenia-like Psychosis**

**Heterogeneous group of disorders:**

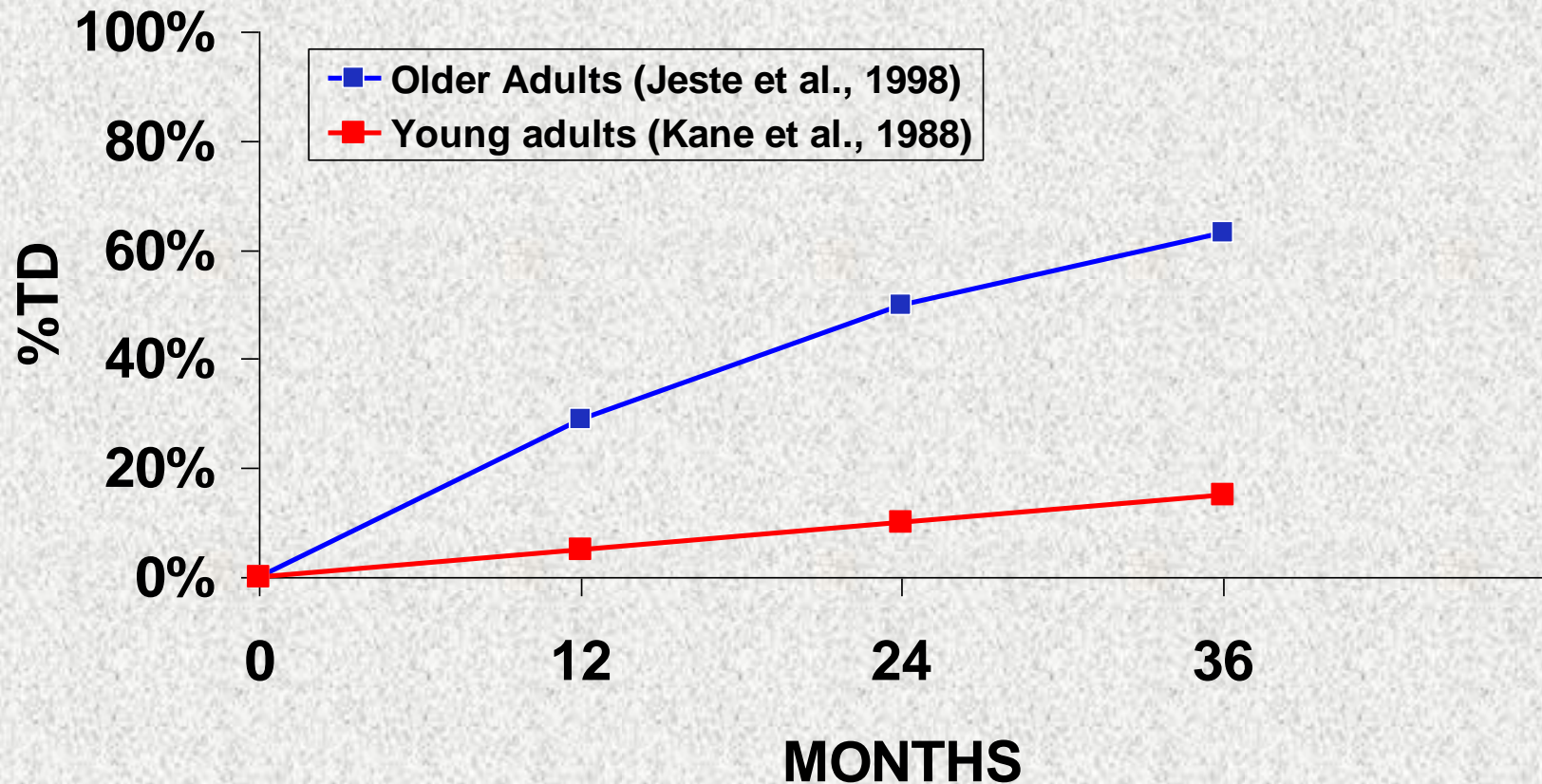
- ❖ **Psychosis of dementia**
- ❖ **Psychosis secondary to general medical conditions or substance use**
- ❖ **Mood disorder with psychotic features**
- ❖ **Delusional disorder**
- ❖ **Psychosis NOS**

# **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)**

# 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.**

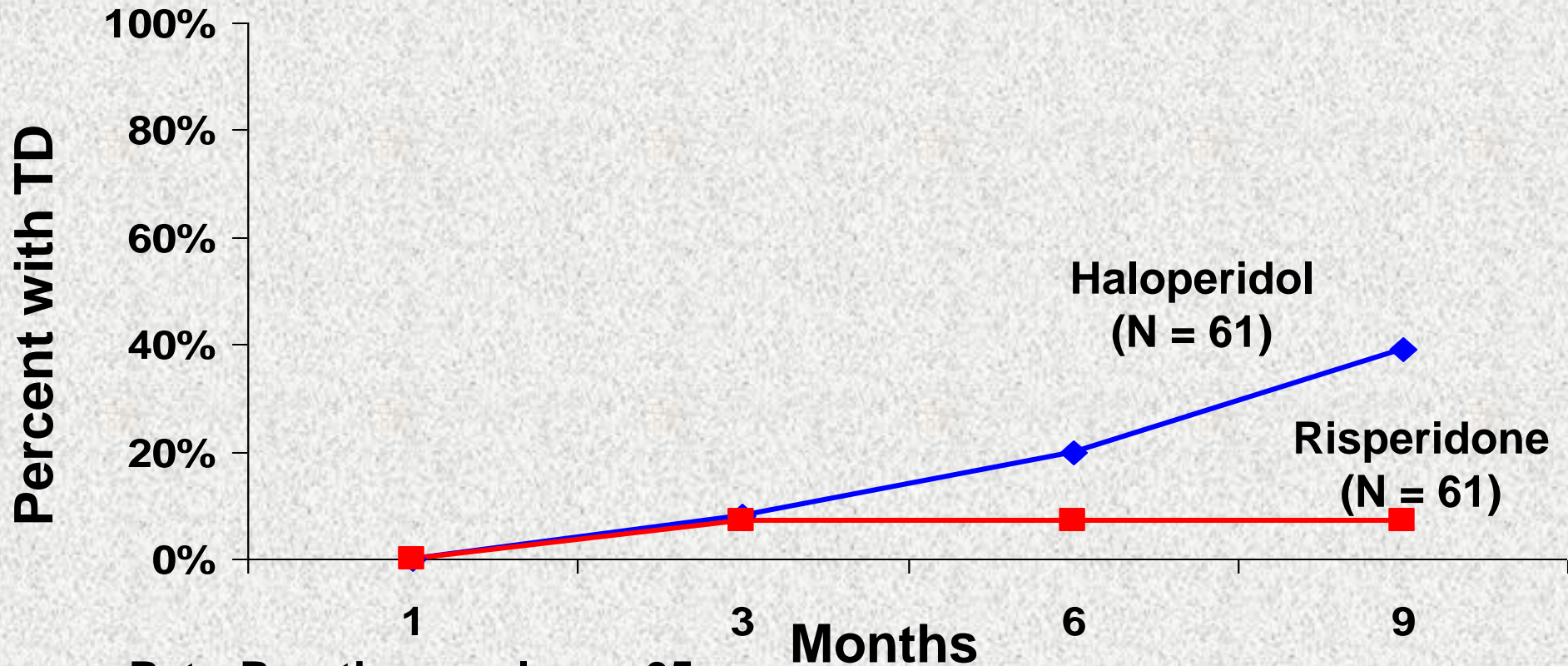
- **International, double-blind, 8-week RCT\***
- **176 patients, aged >60 years**
- **Schizophrenia or schizoaffective disorder**
- **Randomly assigned to flexible doses of Risperidone (1-3; median 2 mg/d) or Olanzapine (5-20; median 10 mg/d)**

# 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)**

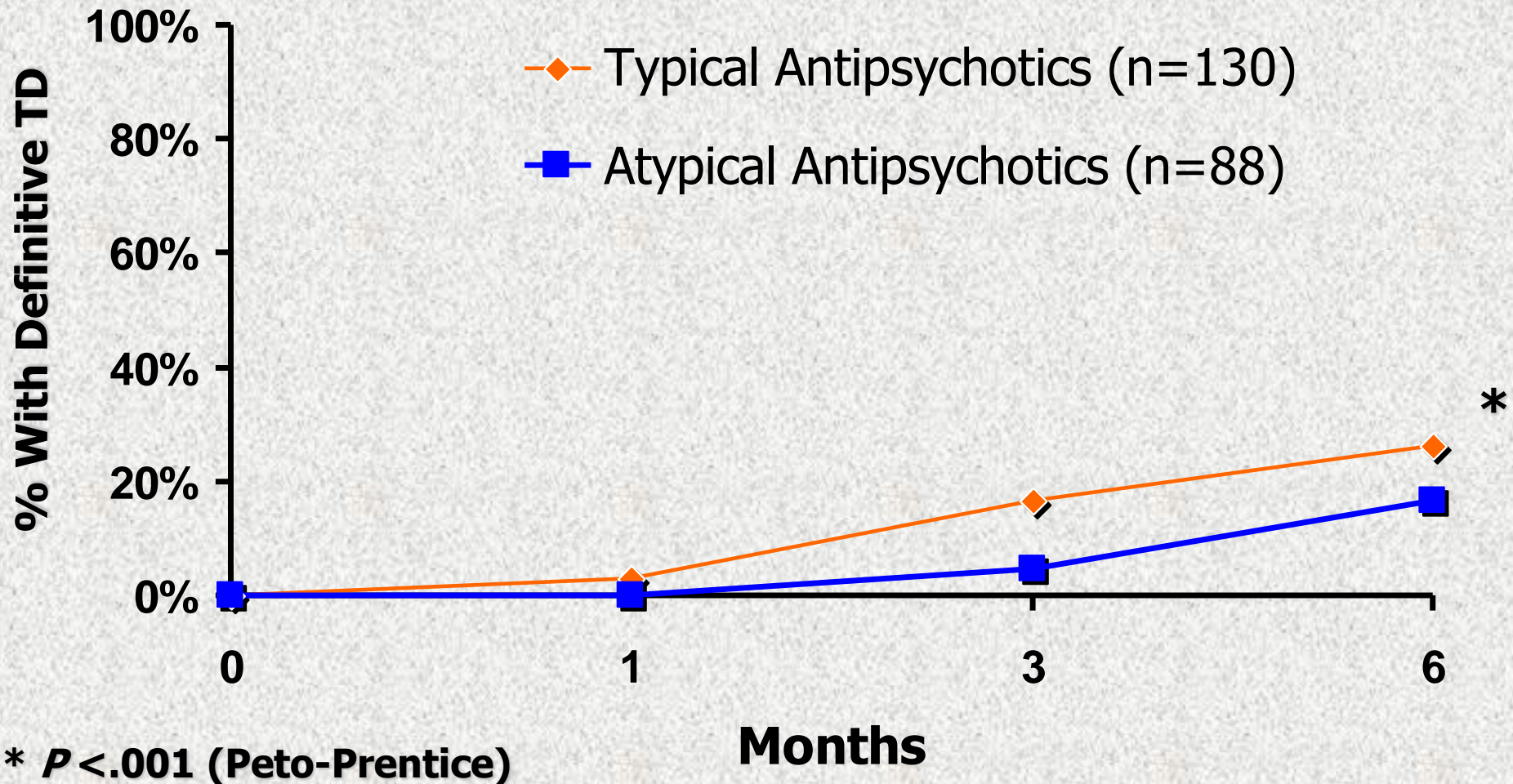


# TD Incidence in Older Patients: Haloperidol versus Risperidone (1mg/d)



Peto-Prentice p-value < .05

# Cumulative Incidence of Definitive TD in Older Patients With Borderline Dyskinesia



# **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 (Brodaty et al., 2003) indicated a higher risk of strokes with risperidone compared to placebo**
- **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**

# **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)

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

# 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**<sup>1</sup>

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”**

# **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**

# **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**

# **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**

# 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 Geriatr 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, Eyer 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**
- **Folsom DP, Depp C, Palmer BW, et al.: Physical and mental health-related quality of life among older people with schizophrenia. Schiz Res 108:207-13, 2009**



## Self-Assessment Question 1

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- 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