

Prevention of Schizophrenia

William R. McFarlane, M.D.

Director

Early Detection and Intervention for the Prevention of Psychosis

National Program Office

Robert Wood Johnson Foundation

Center for Psychiatric Research

Maine Medical Center Research Institute

and

Spring Harbor Hospital

Portland, Maine

University of Vermont

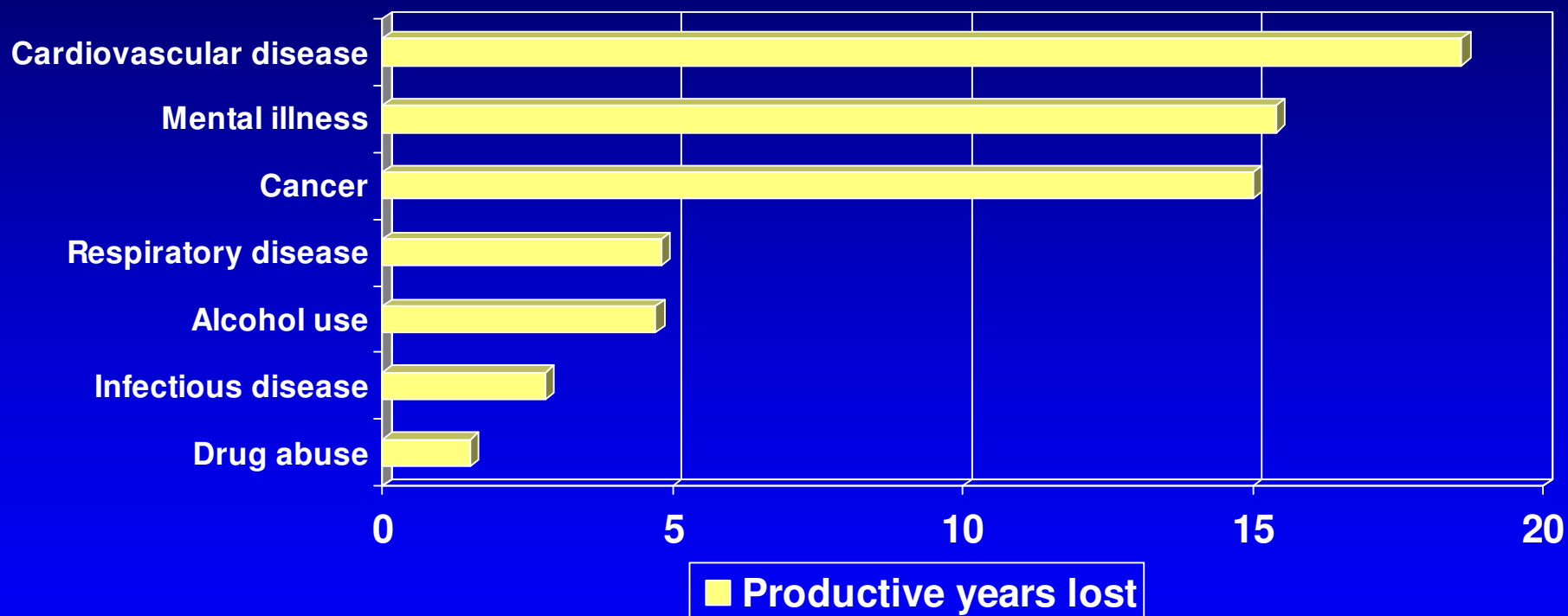
Early detection and prevention in another illness

“If you catch cancer at Stage 1 or 2, almost everybody lives. If you catch it at Stage 3 or 4, almost everybody dies.

We know from cervical cancer that by screening you can reduce cancer up to 70 percent. We’re just not spending enough of our resources working to find markers for early detection.”

**---Lee Hartwell, MD
Nobel Laureate, Medicine
President and Director,
Hutchinson Center
New York Times Magazine
December 4, 2005, p. 56**

Shortened productive lives



Source: Mental Health Report of the Surgeon General

\$10 million

Lifetime costs for each new case of
schizophrenia

25%

Proportion of hospital beds occupied by,
and disability payments to, people with
severe mental disorders

25%

Proportion of people who have only one episode of schizophrenia without developing disability

10-15%

Proportion of people with schizophrenia
who are gainfully employed

2-3%

Proportion of youth who develop
schizophrenia or a severe, psychotic
mood disorder

12-15%

Proportion of people with schizophrenia
or a psychotic mood disorder who commit
suicide

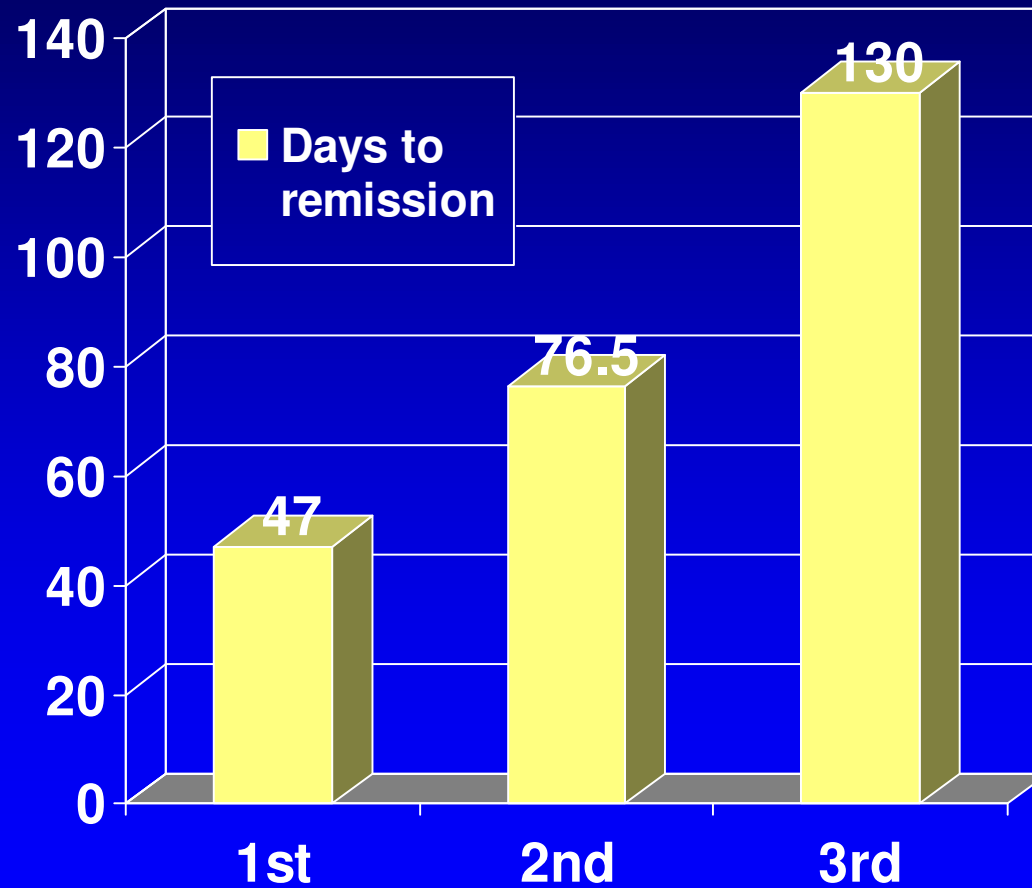
25

Years of life lost by people with schizophrenia due to all causes, including heart disease, cancer and suicide

EMPIRICAL EVIDENCE FOR A RELATIONSHIP BETWEEN A LONG DUP AND A POOR PROGNOSIS

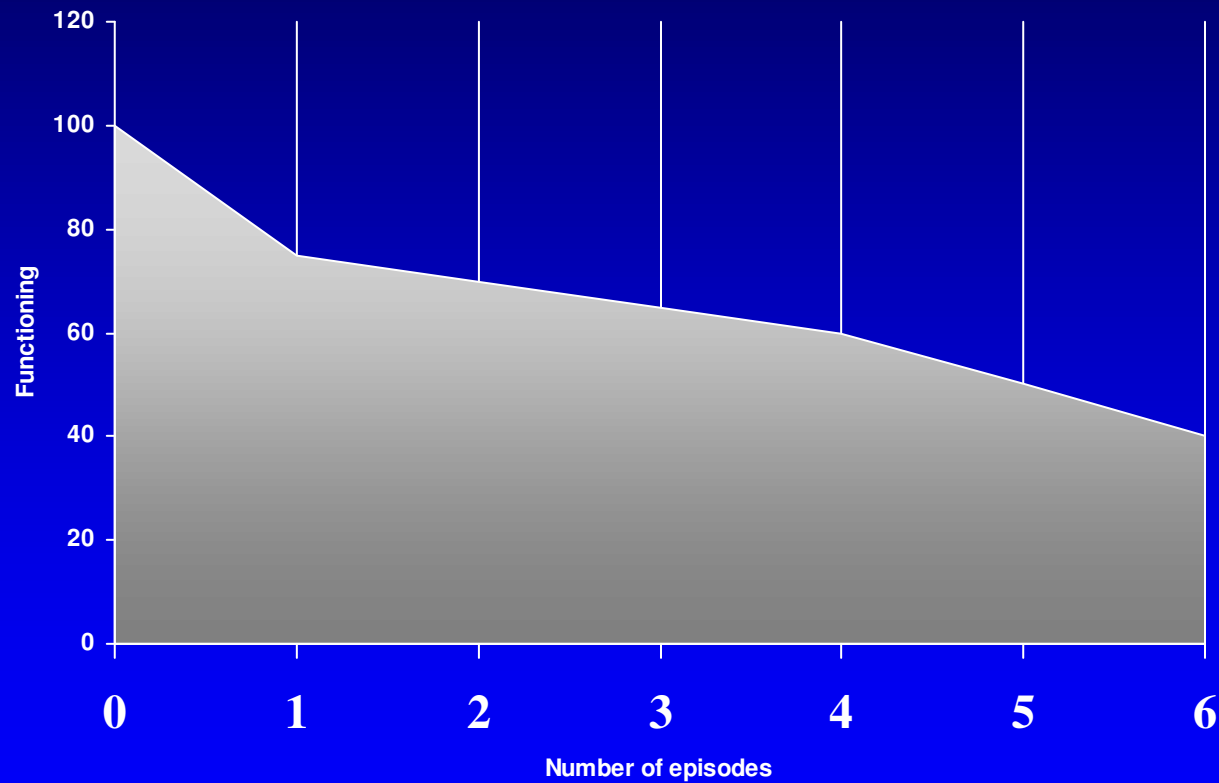
- Johnstone et al. 1986: Many psychotic patients did not get appropriate treatment early, even when they sought help.
- Crow et al. 1986: DUP more important for the course than maintenance medication.
- Rabiner et al 1986: Long DUP was related to a poor one year outcome.
- Wyatt 1991, Opjordsmoen 1991: Earlier treatment predicted better course.

Effects of multiple relapses

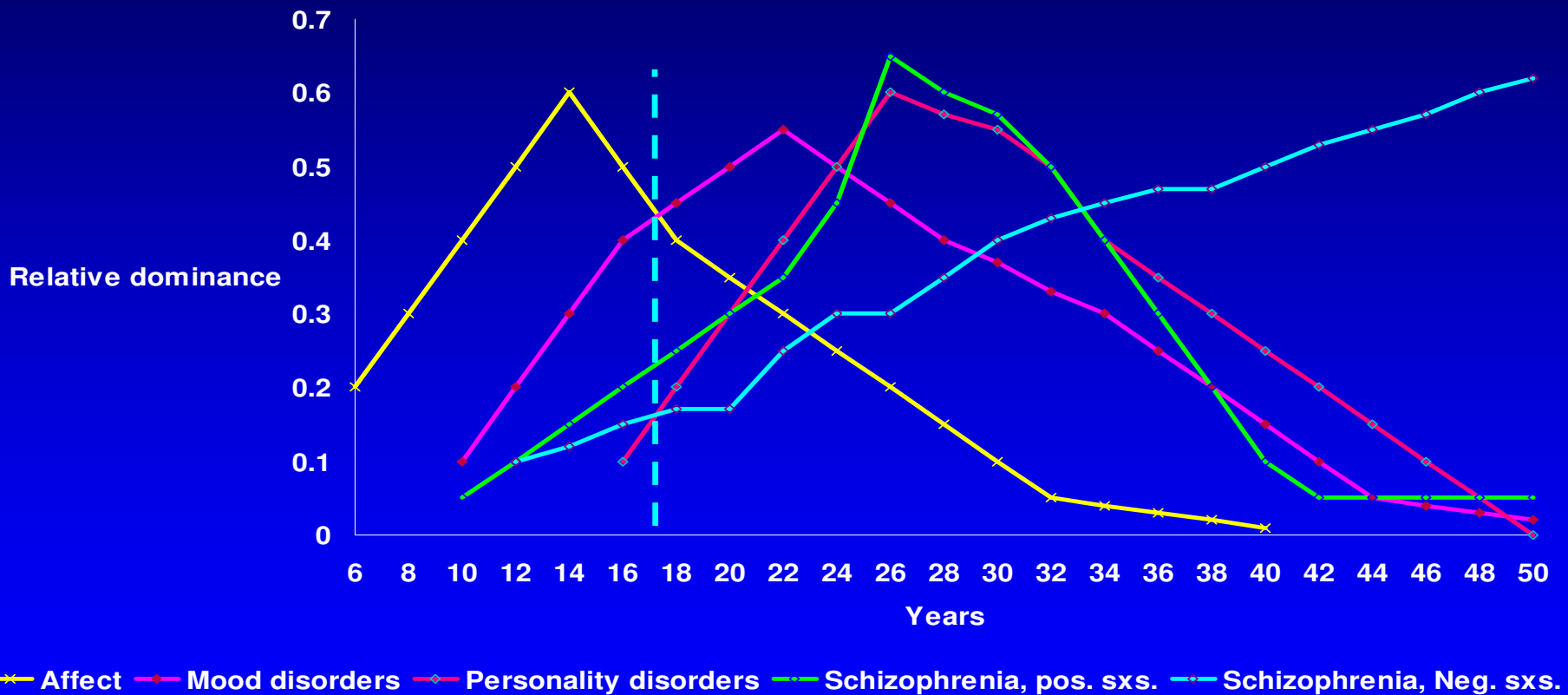


Adapted from Lieberman, J., et al., J Clin, Psychiatry, 1996; 57: 5-9

Functioning as an effect of repeated psychotic episodes

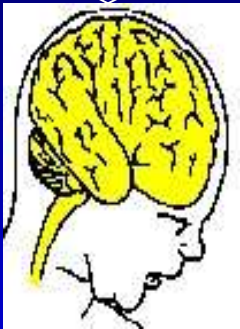


Age of onset of disabling mental illnesses



Early Insults

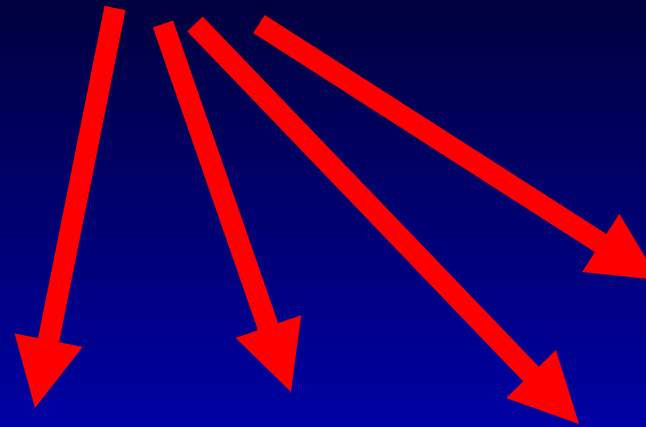
e.g. Disease
Genes, Possibly
Viral Infections,
Environmental
Toxins



**Brain
Abnormalities**

**Structural
Biochemical
Functional**

Social and Environmental Triggers



Biological Vulnerability: CASIS

Increasing Positive symptoms

Disability

**Cognitive
Deficits**

**Affective Sx:
Depression**

**Social
Isolation**

**School
Failure**

ADHD

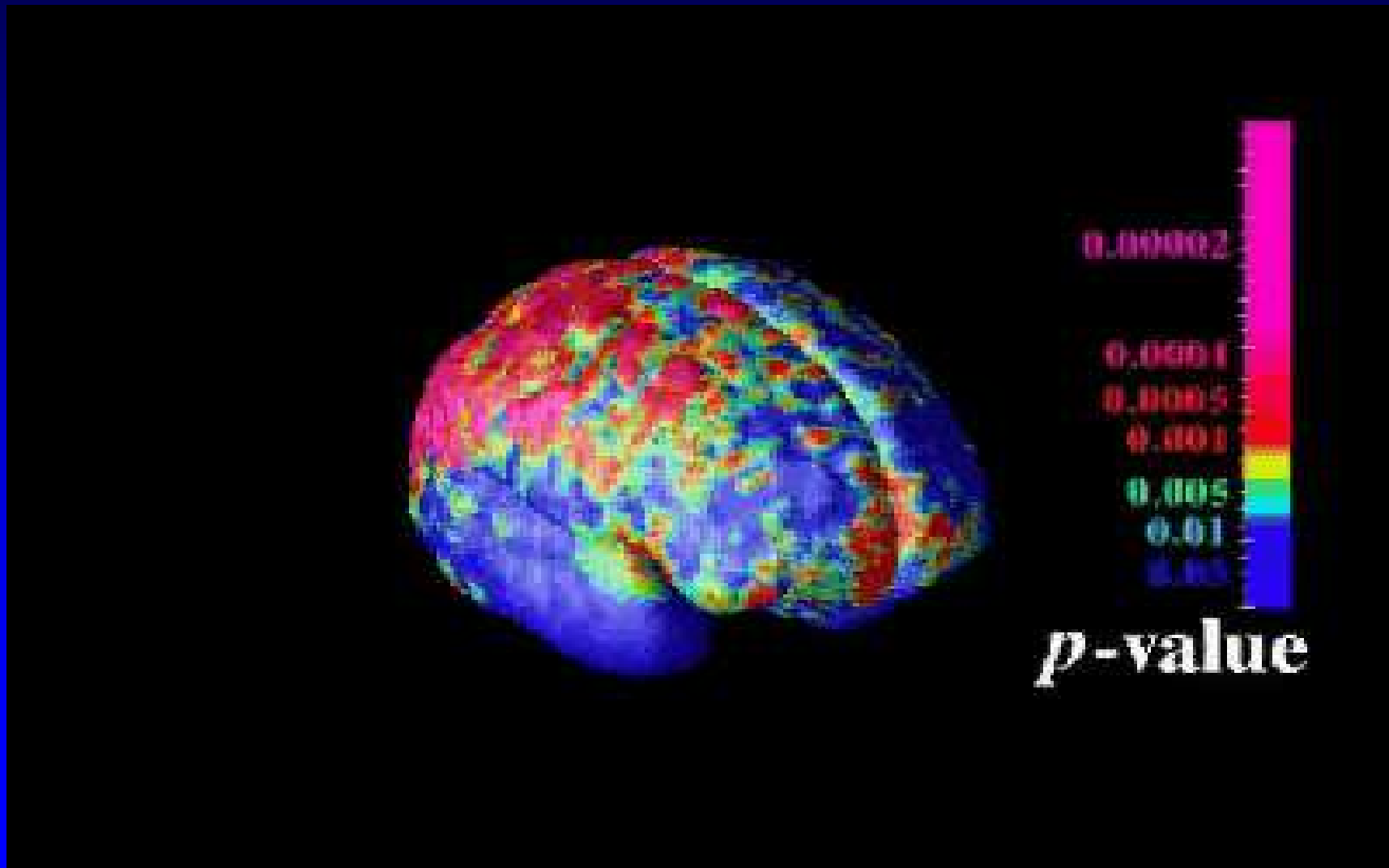
Biologic risk factors

- Genetic risk
 - 80-85% heritability
 - Neuregulin
 - Dystrobrevin binding protein
 - G72, G30
 - RGS4
 - Serotonin receptor gene
 - Dopamine receptor gene
 - COMT
- Non-heritable genetic risk
 - Age of father >50; probably natural mutations in spermatogenesis

Non-genetic biologic and psychosocial risk factors

- Prenatal infections (influenza, rubella, toxoplasma, herpes s.)
- Winter birth
- Prenatal toxic exposure (lead)
- Obstetrical complications
- Head trauma (perinatal to adolescence)
- Autoimmune (Rh incompatibility, thyroid, type 1 diabetes, celiac disease)
- Nutrition (starvation, omega-3 deficiency)
- Heavy metal exposure, maternal/fetal
- Heavy cannabis, other drug exposure
- Urban residence
- Exposure to trauma, with PTSD
- Negative emotional experience

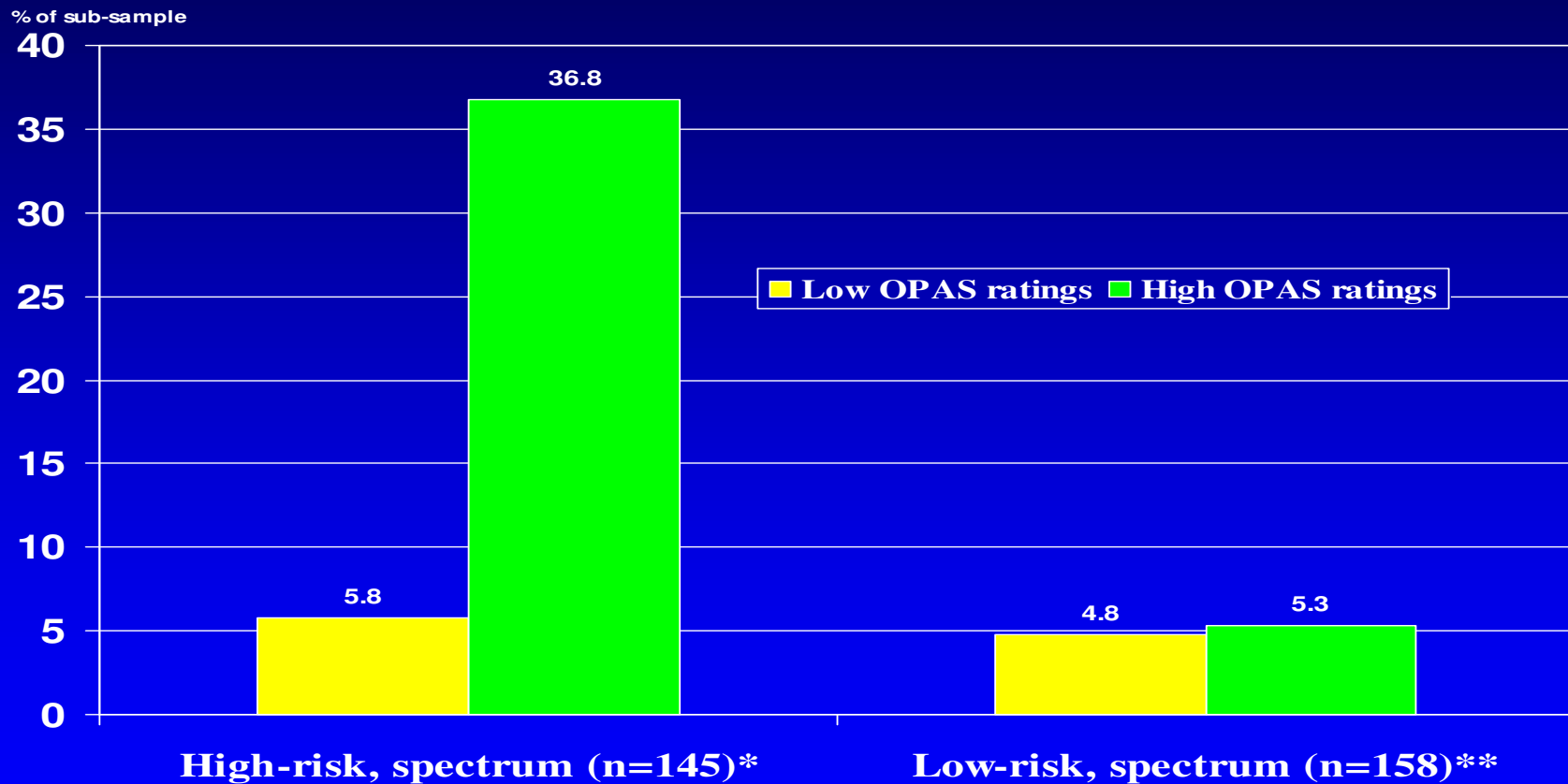
Cortical volume reduction, in childhood-onset schizophrenia, ages 14-19



Pathology and etiology

- **Reduced dendritic spine density, PFC**
- **Lateral and third ventricular enlargement**
- **Overall reduced volume in PFC, hippocampus and superior temporal lobe, progressive prior to and during early phase of illness**
- **Reduced connectivity between grey and white matter**
- **Neurotransmitter abnormalities: dopamine, glutamate and GABA**
- **Partially induced by environmental stress**

Effects of genetic risk and family functioning on eventual schizophrenia-spectrum disorders



* $p < 0.001$

** $p = 0.582$

G X E interaction: $p=0.018$

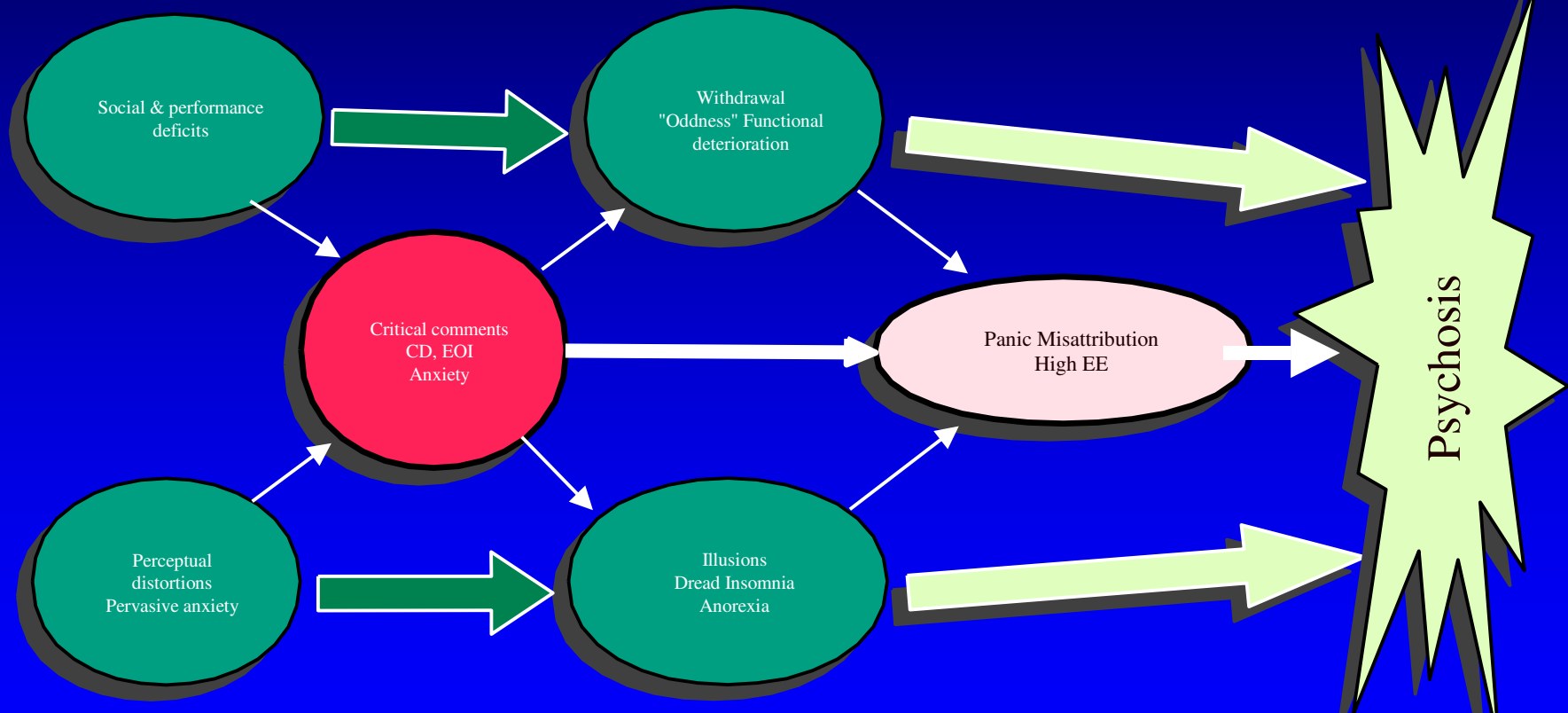
Tienari, Wynne, et al, *BJM*, 2004

Biosocial causal interactions in schizophrenic prodrome

Early prodrome

Late prodrome

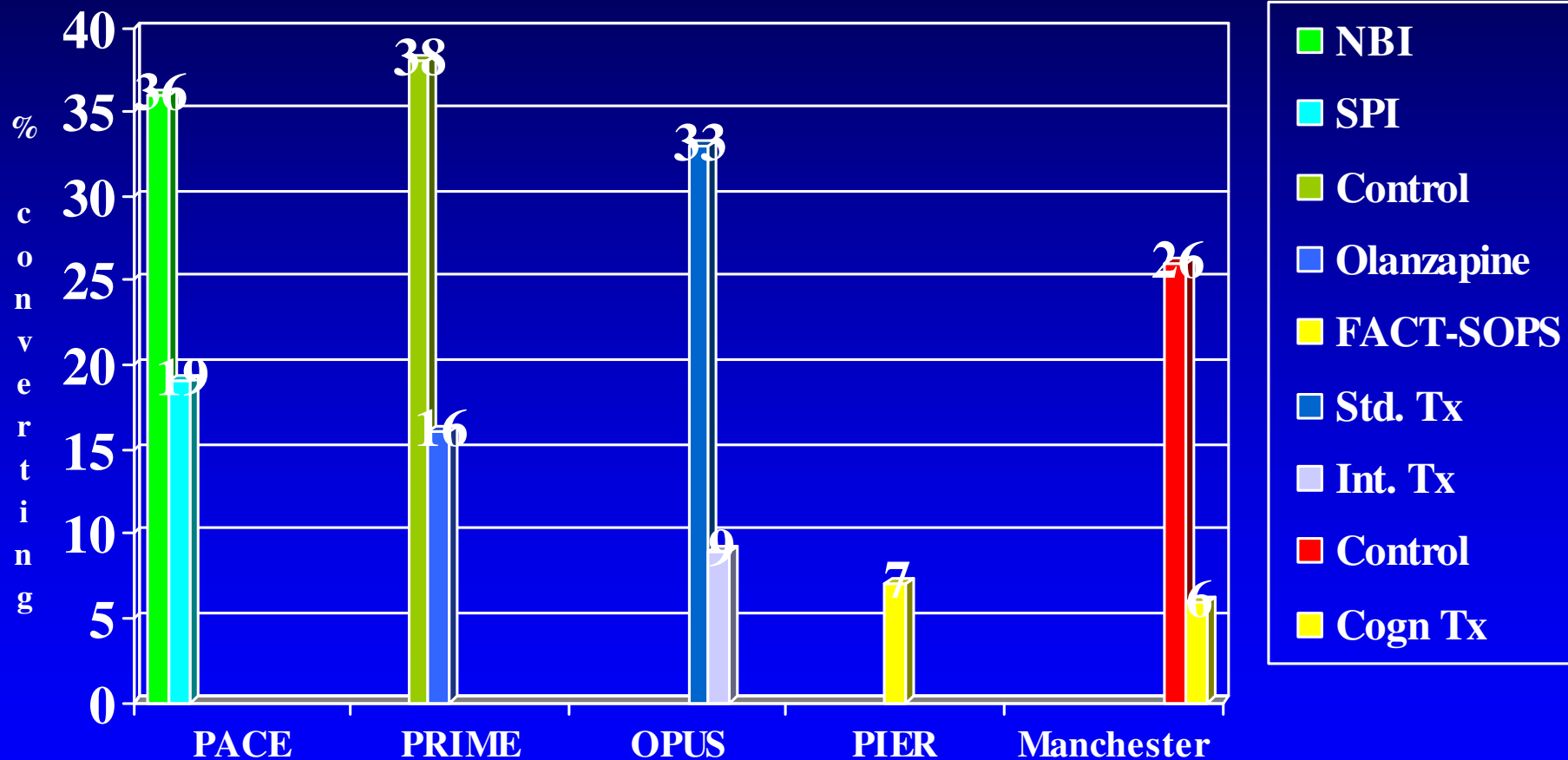
Acute onset



Trials of Indicated Prevention

- **Buckingham, UK**
- **Manchester, UK**
- **German Research Network**
- **OPUS, Denmark**
- **TIPS, Norway, Denmark**
- **PACE, Australia**
- **PRIME, North America**
- **PIER, Maine**
- **EDIPPP, USA**

PACE, PRIME, OPUS and PIER 12 month outcome



Psychosis prevention studies: One year rates for conversion to psychosis

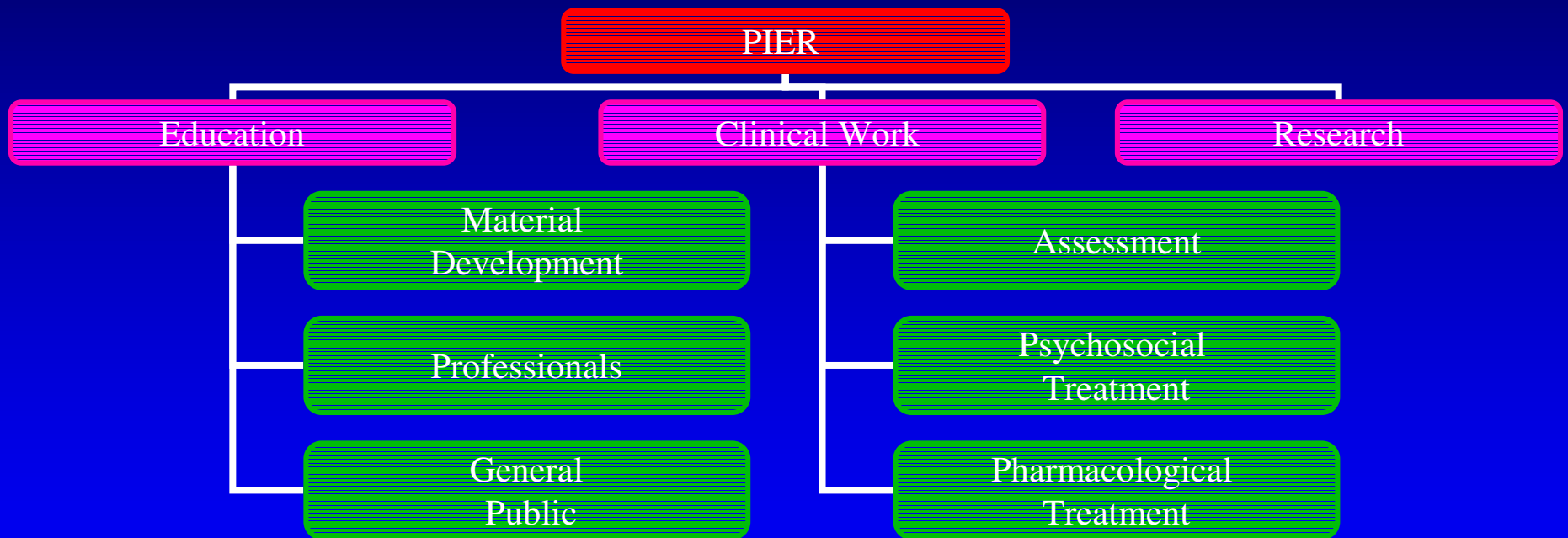
	Control		Experimental	
	n	converted	n	converted
PACE	28	10	31	6
PRIME	29	11	31	5
OPUS	30	10	37	3
Manchester	23	6	35	2
PIER	0	0	96	7
Total	110	37	230	23
Conversion rate		33.6%		10.0%

Portland Identification and Early Referral (PIER)

Reducing the incidence of major
psychotic disorders in a defined
population, by early detection and
treatment:

Secondary prevention

Project Overview



GREATER PORTLAND AREA
POPULATION 260,000



Professional and Public Education

- Reducing stigma
- Information about modern concepts of psychotic disorders
- Increasing understanding of early stages of mental illness and prodromal symptoms
- How to get consultation, specialized assessments and treatment quickly
- Ongoing inter-professional collaboration



What if it's not "just a phase"?

Young people outgrow many things, but not severe mental illness. Most cases develop after 12 and begin with the following warning signs:

- A drop in performance at school, work, or home
- Increasing social withdrawal and isolation
- Significant changes in behavior or thinking
- A change in how one thinks, feels, hears, or experiences the world

If you or your child show most of these symptoms, seek help as soon as possible. Treatment is available, and early intervention may prevent an illness.

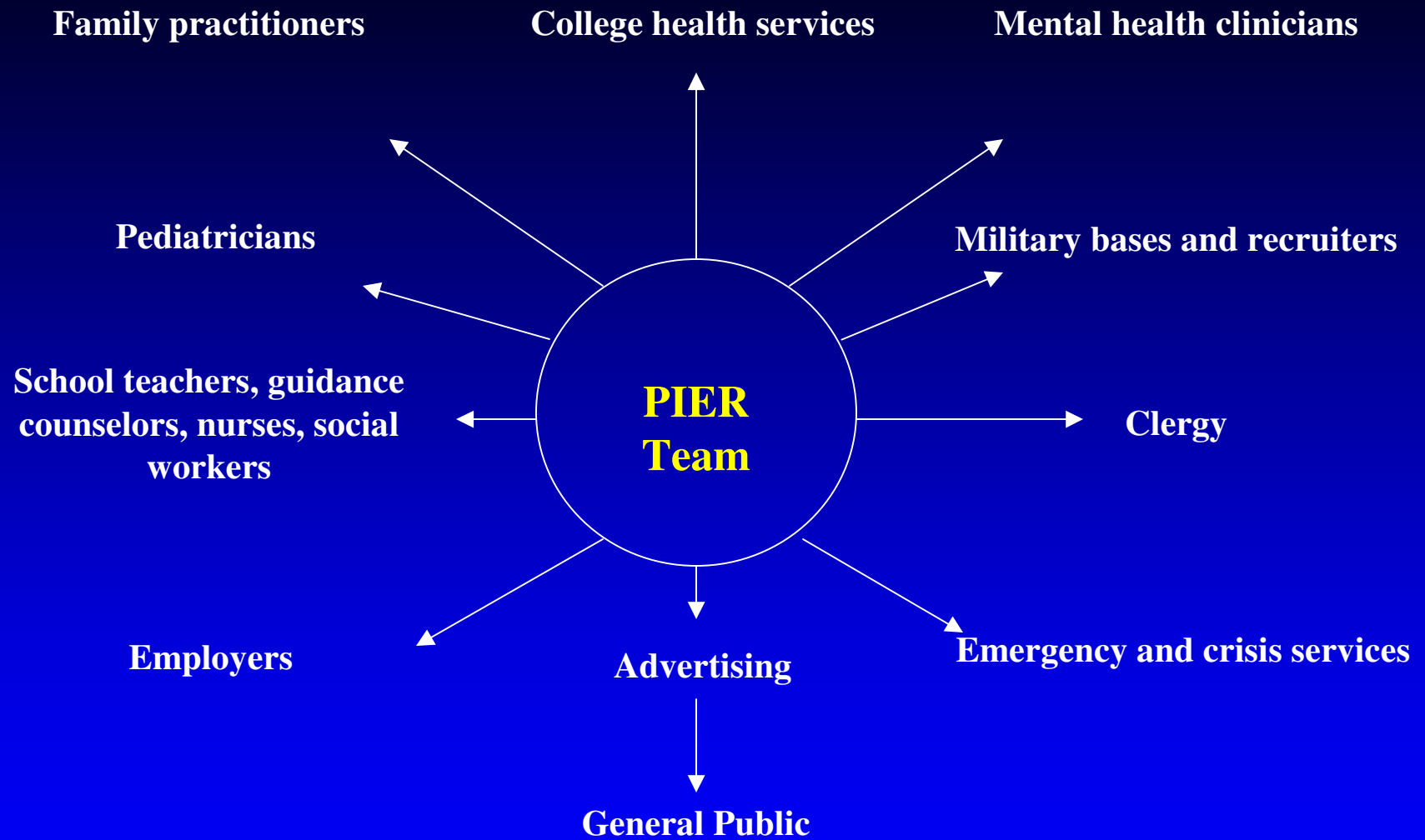
For more information,
call 1-877-880-3377.

The **PIED** Program

"an ounce of prevention"


Maine Medical Center

The MaineHealth® Family



Family practitioners

College health services

Mental health clinicians

Pediatricians

Military bases and recruiters

School guidance
counselors, nurses, social
workers

**PIER
Team**

Clergy

Employers

Emergency and crisis services

General Public

Clinical Strategies

Signs of prodromal psychosis

Schedule of Prodromal Syndrome (SOPS), McGlashan, *et al*

A clustering of the following:

Changes in behavior, thoughts and emotions, with preservation of insight, such as:

Heightened perceptual sensitivity

To light, noise, touch, interpersonal distance

Magical thinking

Derealization, depersonalization, grandiose ideas, child-like logic

Unusual perceptual experiences

“Presence”, imaginary friends, fleeting apparitions, odd sounds

Unusual fears

Avoidance of bodily harm, fear of assault (cf. social phobia)

Disorganized or digressive speech

Receptive and expressive aphasia

Uncharacteristic, peculiar behavior

Satanic preoccupations, unpredictability, bizarre appearance

Reduced emotional or social responsiveness

“Depression”, alergia, anergia, mild dementia

Signs of prodromal psychosis

- 2. A significant deterioration in functioning
 - Unexplained decrease in work or school performance
 - Decreased concentration and motivation
 - Decrease in personal hygiene
 - Decrease in the ability to cope with life events and stressors
- 3. Withdrawal from family and friends
 - Loss of interest in friends, extracurricular sports/hobbies
 - Increasing sense of disconnection, alienation
 - Family alienation, resentment, increasing hostility, paranoia

Other entry criteria

- Ages 12-35
- Brief psychotic episode (< 1 month)
- Prodromal symptoms or recent deterioration (>30% GAF decrease) in youth with a first or second degree relative with a psychotic disorder.
- Schizotypal personality disorder *combined* with recent deterioration (>30% GAF decrease) are also at risk.

Signs of prodromal psychosis

Changes in behavior, thoughts and emotions, with preservation of insight, such as:

Unusual perceptual experiences

“Presence”, shadows, visual trails, ghosts

Imaginary friends

Fleeting apparitions

Odd sounds

Somatic illusions or hallucinations

Heightened or dulled perceptions

Vivid sensory experiences

Sensations and thoughts located outside the body

Frequent distortions or illusions

Brief but frank hallucinations, minimal effect on behavior or thinking

Signs of prodromal psychosis

Changes in behavior, thoughts and emotions, with preservation of insight, such as:

Unusual fears

- Marked guardedness, distrustful
- Fear of assault (not social phobia)
- Avoidance of bodily harm
- Somatic delusions
- Severe nihilism
- Persistent persecutory self-referential thoughts
- Paranoia
- Extreme guilt, fear of harming others
- Bizarre obsessional preoccupations
- Fears of mind-reading
- Frank delusions, without full conviction

Family-aided Assertive Community Treatment (FACT): Clinical and functional intervention

- Rapid, crisis-oriented initiation of treatment
- Psychoeducational multifamily groups
- Case management using key Assertive Community Treatment methods
 - Integrated, multidisciplinary team; outreach PRN; rapid response; continuous case review
- Supported employment and education
- Collaboration with schools, colleges and employers
- Cognitive assessments used in school or job
- Low-dose atypical antipsychotic medication
 - 10-20 mg aripiprazole, 2.5-7.5 mg olanzapine, 0.25-3 mg risperidone
- Mood stabilizers, as indicated by symptoms:
 - SSRIs, with caution, especially with aripiprazole and/or a family history of manic episodes
 - Mood stabilizing drugs: lamotrigine 50-150 mg, valproate, 500-1500mg, lithium at therapeutic doses by blood level, 0.6-1.2

Key clinical strategies in family intervention specific to prodromal psychosis

- Strengthening relationships and creating an optimal, protective home environment:
 - Reducing intensity, anxiety and over-involvement
 - Preventing onset of negativity and criticism
 - Adjusting expectations and performance demands
 - Minimizing internal family stressors
 - Marital stress
 - Sibling hostility
 - Conceptual and attributional confusion and disagreement
 - Buffering external stressors
 - Academic and employment stress
 - Social rejection at school or work
 - Cultural taboos
 - Entertainment stress
 - Romantic and sexual complications

PIER: Outcomes after one year of treatment

Data for 96 at-risk cases from the first 4 years intake:

n = 96

Intake: May 7, 2001- May 6, 2005

PIER referral sources

Referral source (n = 492)	%
Family	26.4
School, college professionals	18.9
Mental health agencies	18.1
In-house (MMC, SHH)	19.7
Community physicians, therapists	13.8
Self	1.2
Other	1.8

Screening and treatment entry

Referrals	505	
SIPS Completed	140	27.7%
Met SOPS Criteria	65	46.4%
Declined treatment	7	10.7%
Dropped out <3 Months	3	4.6%
Treated sample	55	84.6%

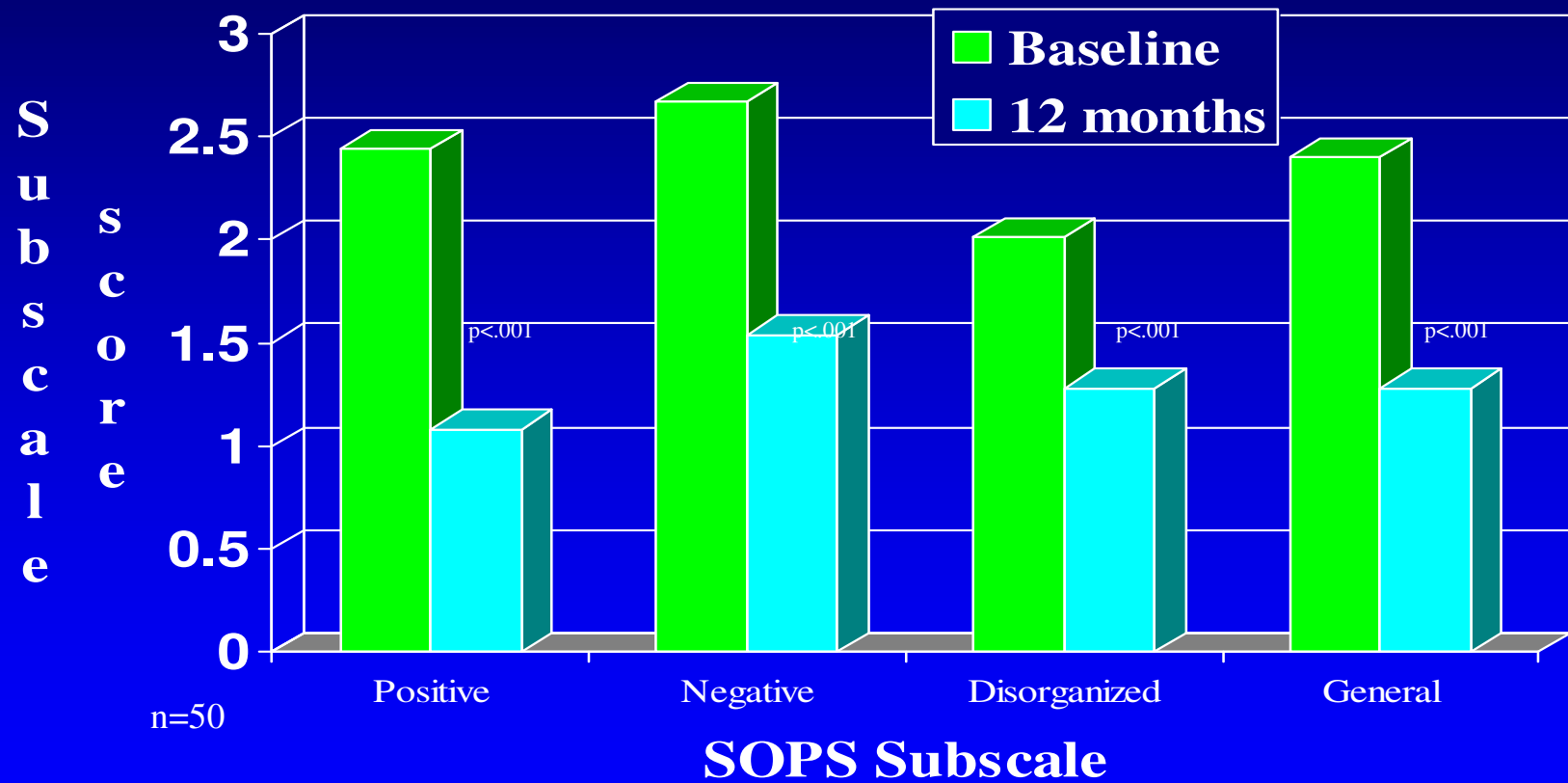
Demographics of the treated sample

Males (age range 12 - 27)	57%
Females (age range 12 - 24)	44%
Average age	16

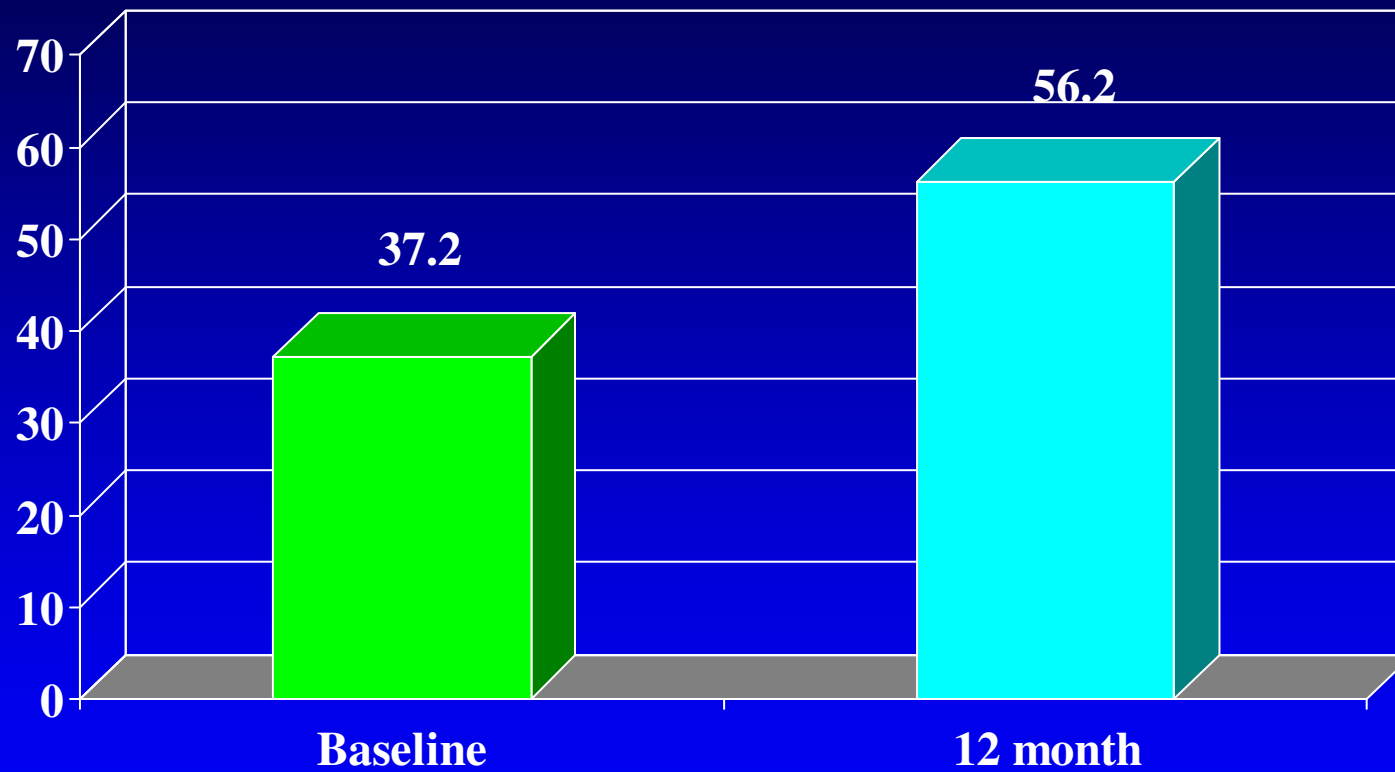
Treated cases converting to psychosis

• Cases not converted	82	86%
• Cases converted, 1-6 days	4	4%
• Cases converted, 7-30 days	3	3%
• SOPS psychosis conversions	3	3%
• Schizophrenic disorder	4	4%

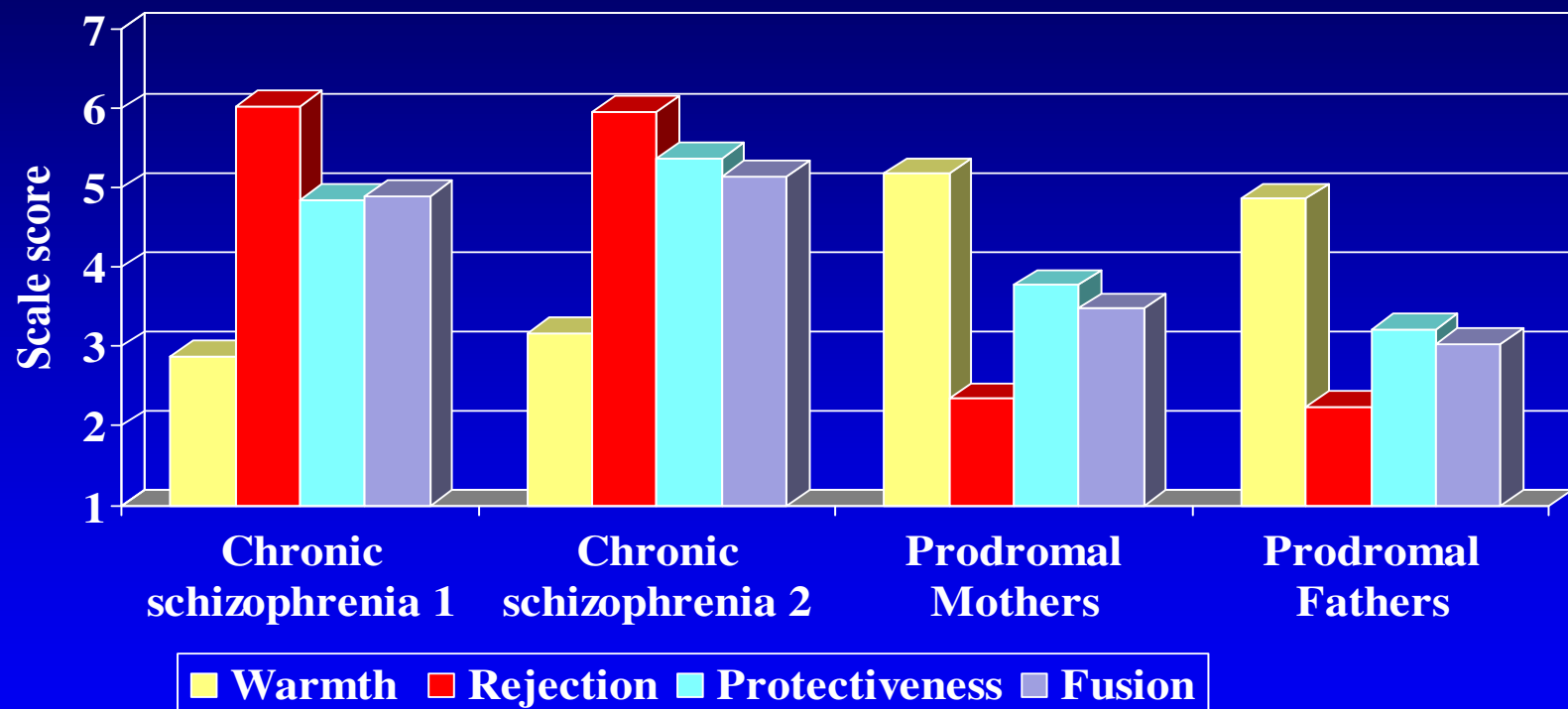
SOPS scores at baseline and 12 months



Overall functioning: Baseline and 12 months

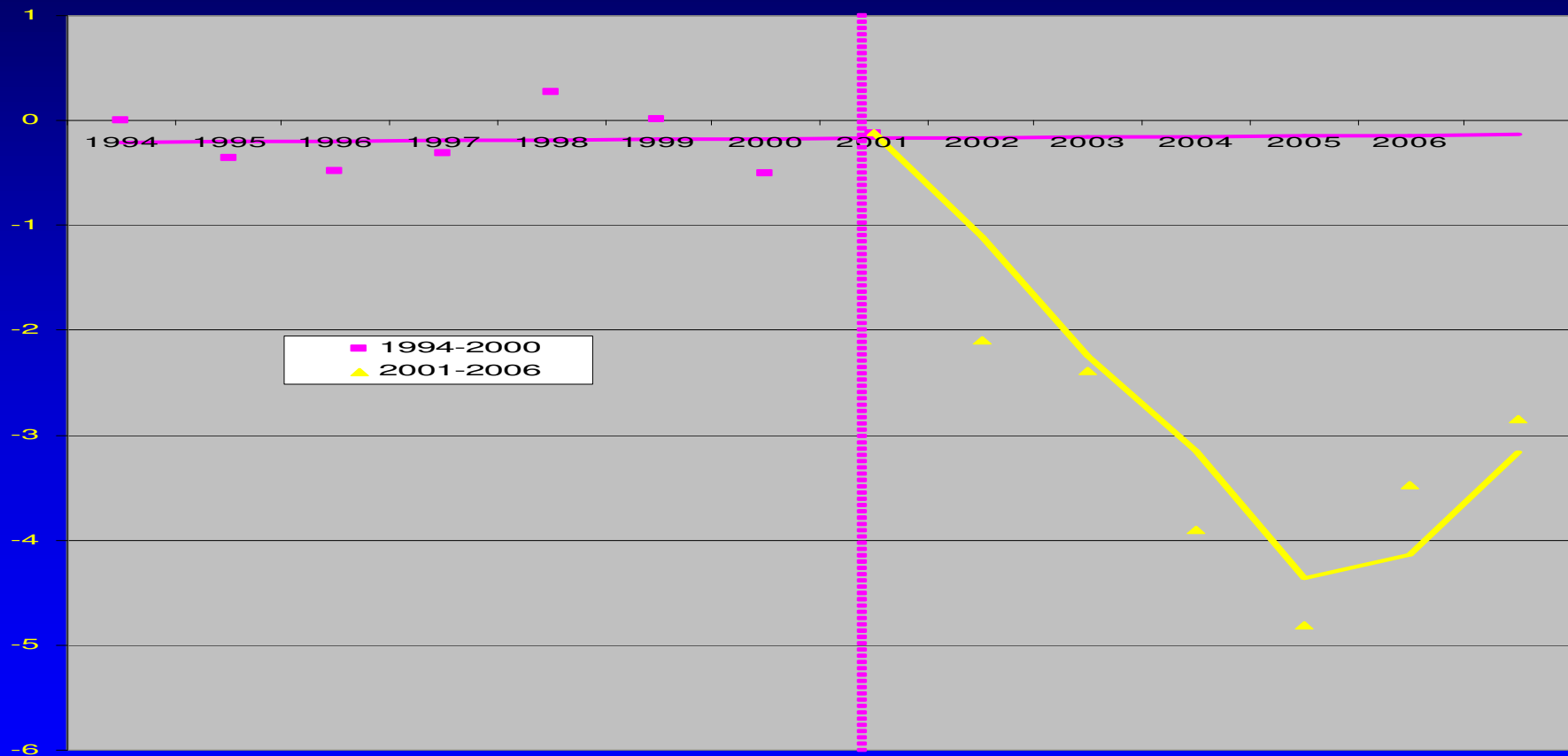


Components of expressed emotion: Prodromal vs. chronic phase

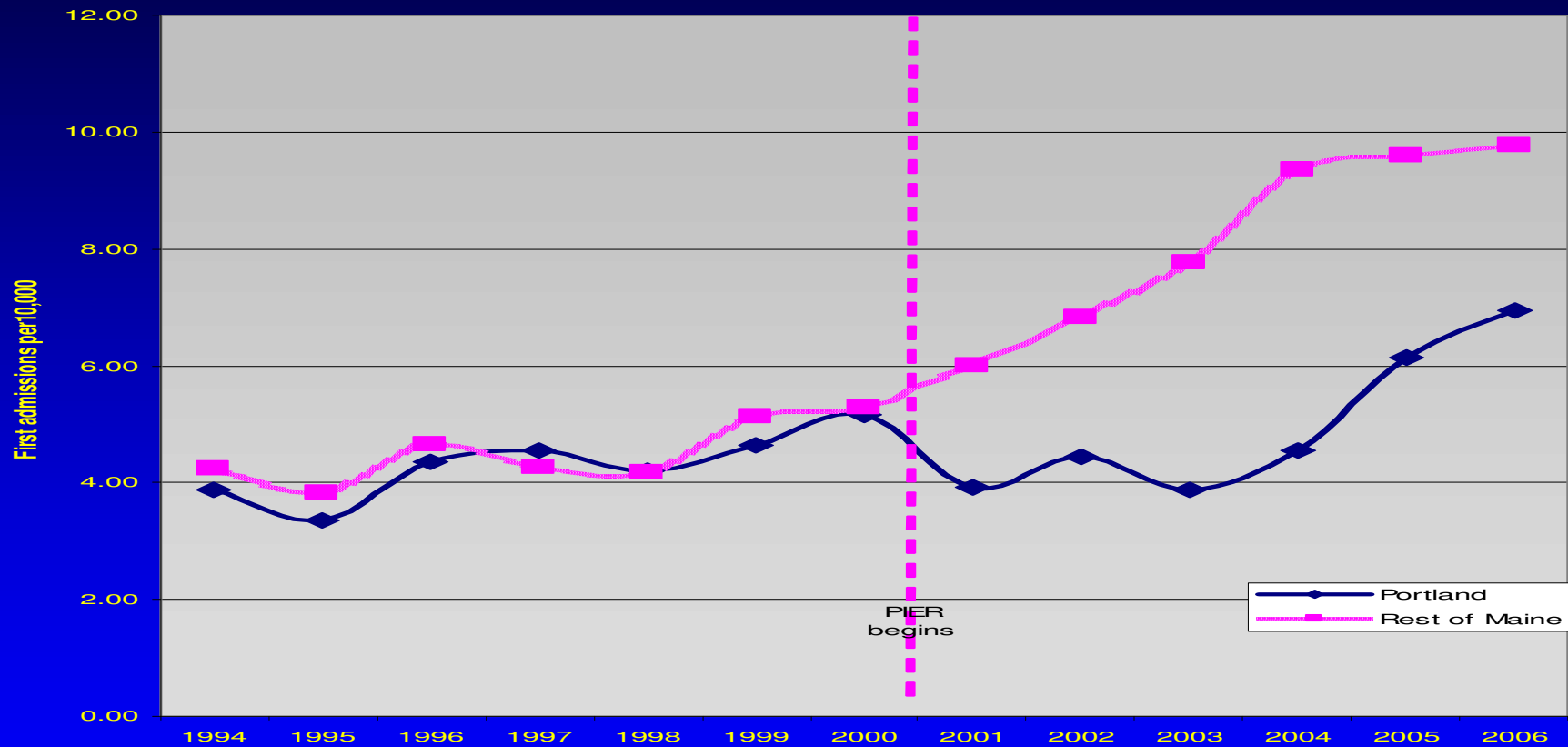


All differences, prodromal vs. chronic: $p < 0.01$

Difference in first hospitalizations per 10,000 population for psychosis, age 12-35 Greater Portland vs. rest of Maine, 1994-2006



First hospitalizations for psychosis Greater Portland vs. rest of Maine



Schizophrenia: Differences from expected incidence rates Portland vs. Rest of Maine

Diagnosis Group:
DSMIV Schizophrenia

	mean	s.d.	Difference, Portland vs. Rest of Maine
Portland, pre PIER	1.240	0.257	
Rest of Maine, pre-PIER	1.034	0.219	+120%
Portland, PIER	1.17	0.330	
Rest of Maine, 2001-2004	1.58	0.188	-74%
Difference, %			-46%

*1999 *not* adjusted for JBI admission closure

Differences between treated prodromal and post-psychotic states

Prodromal young persons have manifested:

- Maintenance of insight (prevention of loss)
- Continued dysphoric/ego-dystonic response to prodromal/psychotic symptoms
- High acceptance of, and adherence to, treatment
- Low rates of substance abuse
- More open to discontinuing heavy drug and alcohol abuse
- Less resistance to family inclusion by patient
- Stronger family involvement
- Higher motivation to continue schooling and/or work
- More trusting and grateful therapeutic relationships
- Higher sensitivity to treatments
- Higher likelihood of improving course of functioning

Early Detection and Intervention for the Prevention of Psychosis

- Effectiveness Trial at five sites:
 - Portland, Maine (MMC)
 - Glen Oaks, New York (AECOM)
 - Ann Arbor, Michigan (UM)
 - Salem, Oregon (OHSU)
 - Sacramento, California (UCD)
- Sponsored by RWJF
- Regression discontinuity and incidence reduction
- Large and diverse sample
- Community outreach and identification systems
- Basis for dissemination

North American Prodromal Longitudinal Study

- Follow-along after careful baseline assessment for prodromal syndrome
- Sponsored by NIH
- ~90% will have naturalistic outcomes
- N=888, 370 have elevated risk, 174 help-seekers, 195 non-psychiatric controls
- Many psychosocial, cognitive and biological measures

Improved identification

- Smell and other sensory tests
- Thought disorder test
- Key tests of working memory, executive function and verbal memory and processing
- MRI evidence of volumetric loss, ventricular enlargement and grey-to-white matter ratio shift

Improved treatment

- **Alternative biological interventions**
 - **SSRI drugs**
 - **Omega-3 FAs**
 - **Glutamatergic amino acids or drugs**
- **Cognitive rehabilitation**

Primary prevention: Universal and selective

- Prenatal and perinatal care
 - Assess for and prevent:
 - Rh, lead, infection, brain trauma, maternal psychosocial stress, family history of schizophrenia, older parents
 - Vaccination, hyper-oxygenation, early super-nutrition for high risk fetuses
 - Assessment and intervention for fetuses with enlarged ventricles
- Very early—premorbid—identification
 - Family psychoeducation and prevention of isolation
 - Compensatory education and cognitive rehabilitation
 - Cognitive-enhancing agents
 - Stem-cell implants?

What's needed

- Redefinition of “medical necessity”
 - Prodromal psychosis, by empirical criteria
 - Criteria for eligibility for prevention services
- Standards and licensing for early detection and prevention treatment services
- Partnership with large insurers
 - To prevent growing burden of mental health service costs
- Intensive treatment by supervised practitioners for 2 years
 - Probably routine services after that
- Training, consultation and supervision of services to achieve practice standards
- Professional education by each participating service team
 - About six months of outreach, training, consultation, trial assessments
- Public education, using economies of scale as in the stop-smoking campaign.

Conclusions

- Public education is beginning to influence attitudes, knowledge and behavior.
- Increasingly accurate referrals are coming from outside the mental health system.
- Number needed to treat is equal to or better than for other medical indicated preventive interventions
- Medication at low doses is adequate but appears essential for prevention of imminent, and perhaps later, psychosis.
- Very low conversion rates accompany evidence-based, comprehensive treatment (~15%; ~5% for schizophrenic disorders).
- A substantial proportion of the incident population can be identified and prevented from developing psychosis, in the short term.
- Improved identification and treatment will improve the rates for both false-positives and conversion to psychosis
- Further testing is needed.
- A major national campaign will be mounted in the next decade