

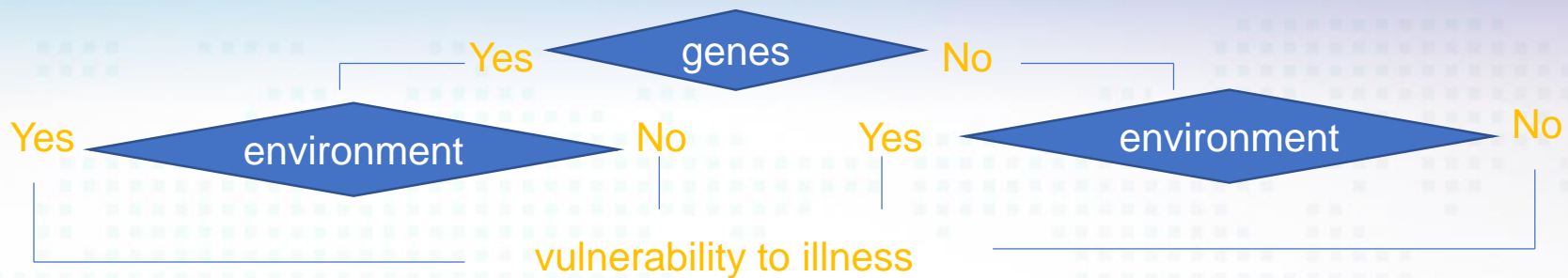


西部精神医学  
四川省西部精神医学协会

# SCHIZOPHRENIA: Early Detection/Prevention

William T. Carpenter, M.D.  
Professor of Psychiatry and Pharmacology  
University of Maryland School of Medicine  
Department of Psychiatry  
Maryland Psychiatric Research Center



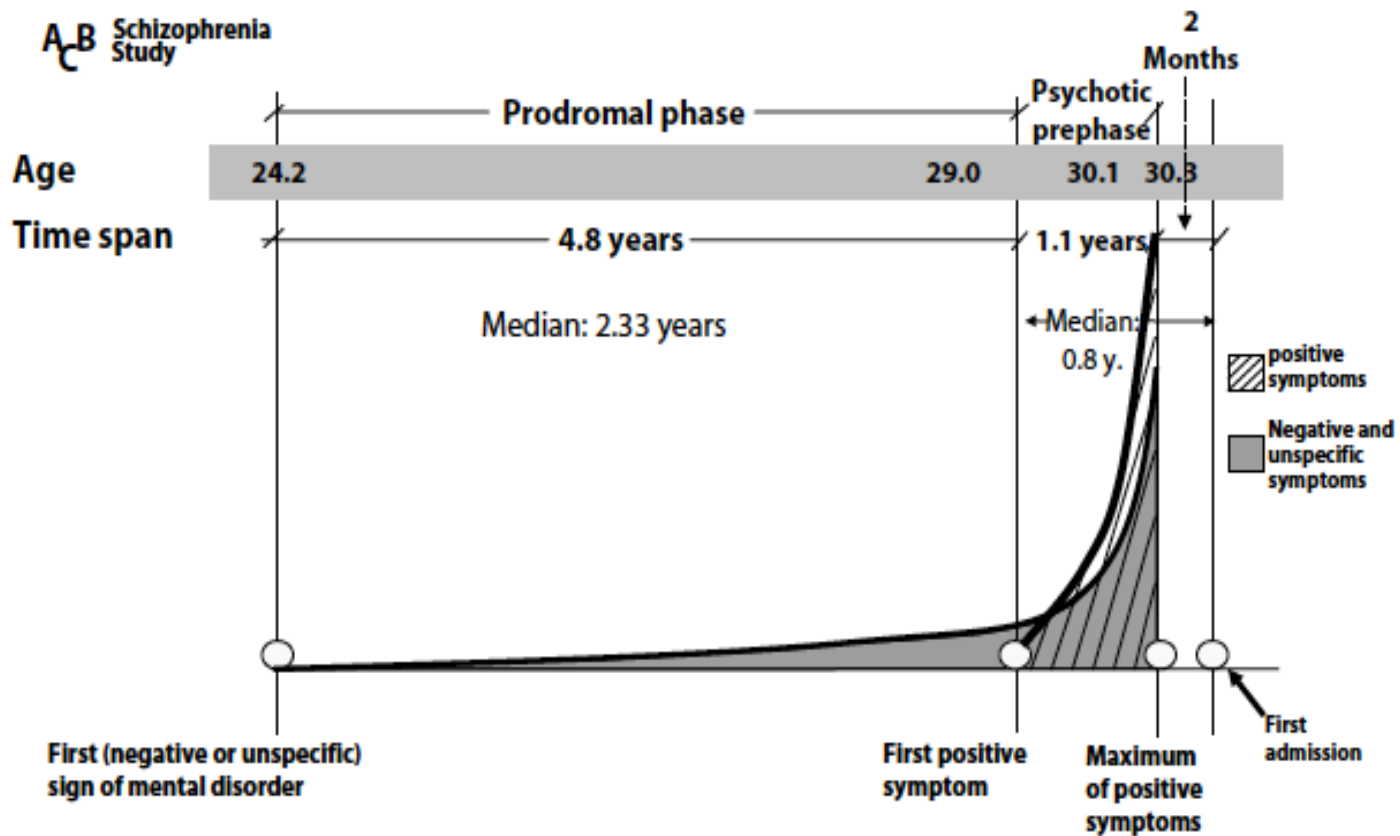


vulnerability to schizophrenia

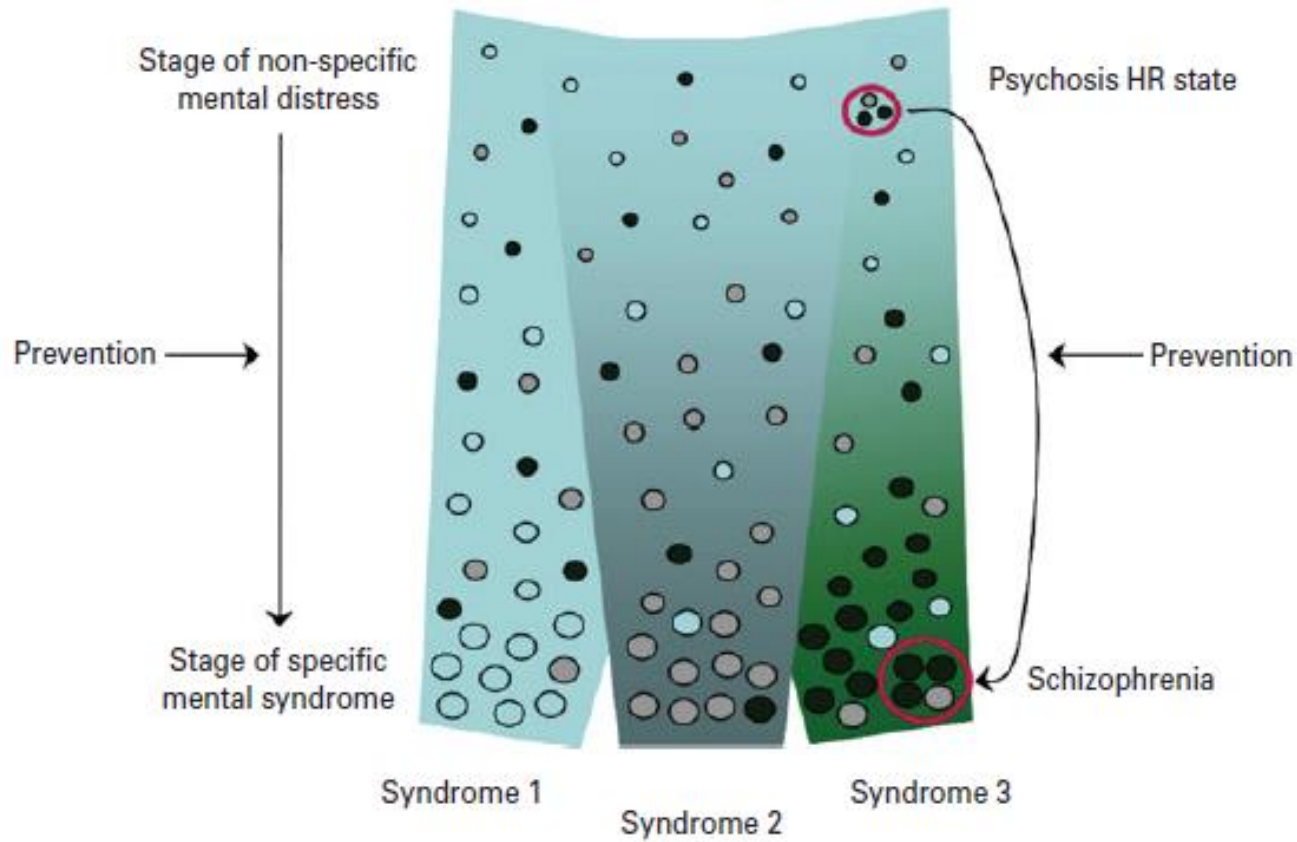


schizophrenia





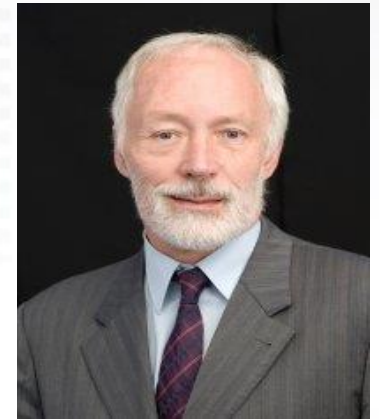
# Clinical High Risk



# At Risk Mental State

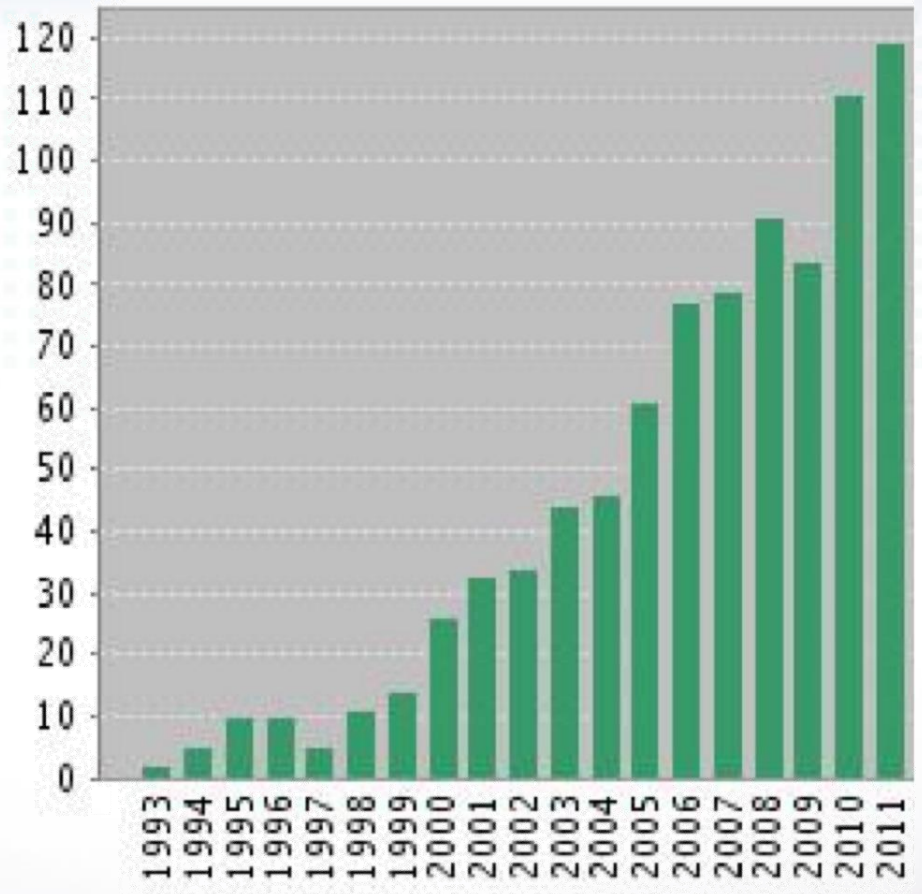


- Basic Symptom
- Schizophrenia prodrome
- BLIPS-Brief limited intermittent psychosis
- UHR-Ultrahigh risk
- CHR-Clinical high risk
- APS-Attenuated psychosis syndrome



Ian Falloon







# Criteria for the Attenuated Psychotic Symptom Syndrome

A. At least one of the following symptoms are present in attenuated form, with relatively intact reality testing, and are of sufficient severity or frequency to warrant clinical attention:

1. Delusions
2. Hallucinations
3. Disorganized speech

B. Symptom(s) must have been present at least once per week for the past month.

C. Symptom(s) must have begun or worsened in the past year.



# Criteria for the Attenuated Psychotic Symptom Syndrome (continued)

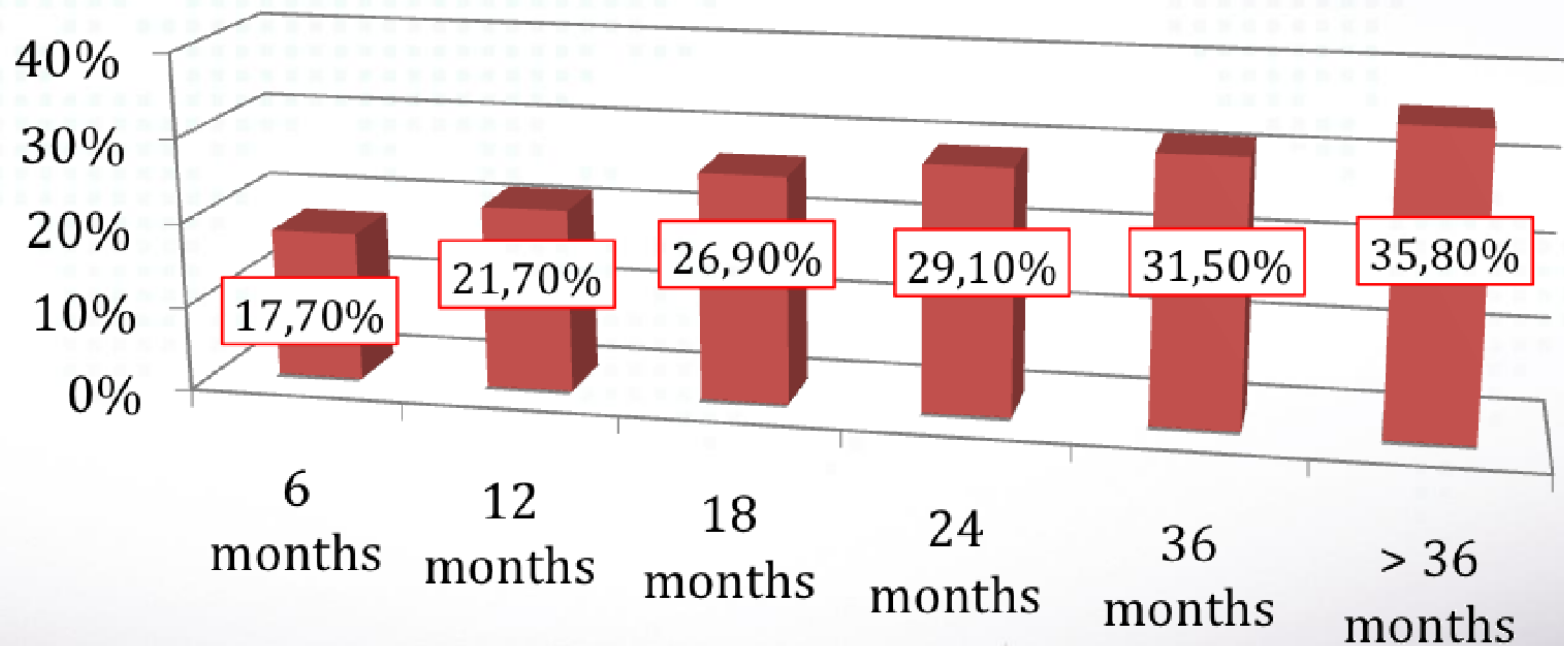
- D. Symptom(s) are sufficiently distressing and disabling to the individual to warrant clinical attention.
- E. Symptom(s) are not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and are not attributable to the physiological effects of a substance or another medical condition.
- F. Criteria for any psychotic disorder have never been met





# 30% TRANSITION RISK AT 2 YRs

Meta-analysis of transition outcomes in 2500 HR subjects



# ICD/DSM diagnostic outcomes in transitions (n=560)



- Other psychoses
- Schizophrenia spectrum disorders
- Mood disorders with psychosis



# APS: a Validated Disorder

1. Distress
2. Dysfunction
3. Gray matter reduction
4. White matter reduction
5. Electrophysiology
6. Cognition impairment
7. Negative symptoms
8. Transition to psychosis
9. Schizophrenia spectrum



# Predictors of Transition

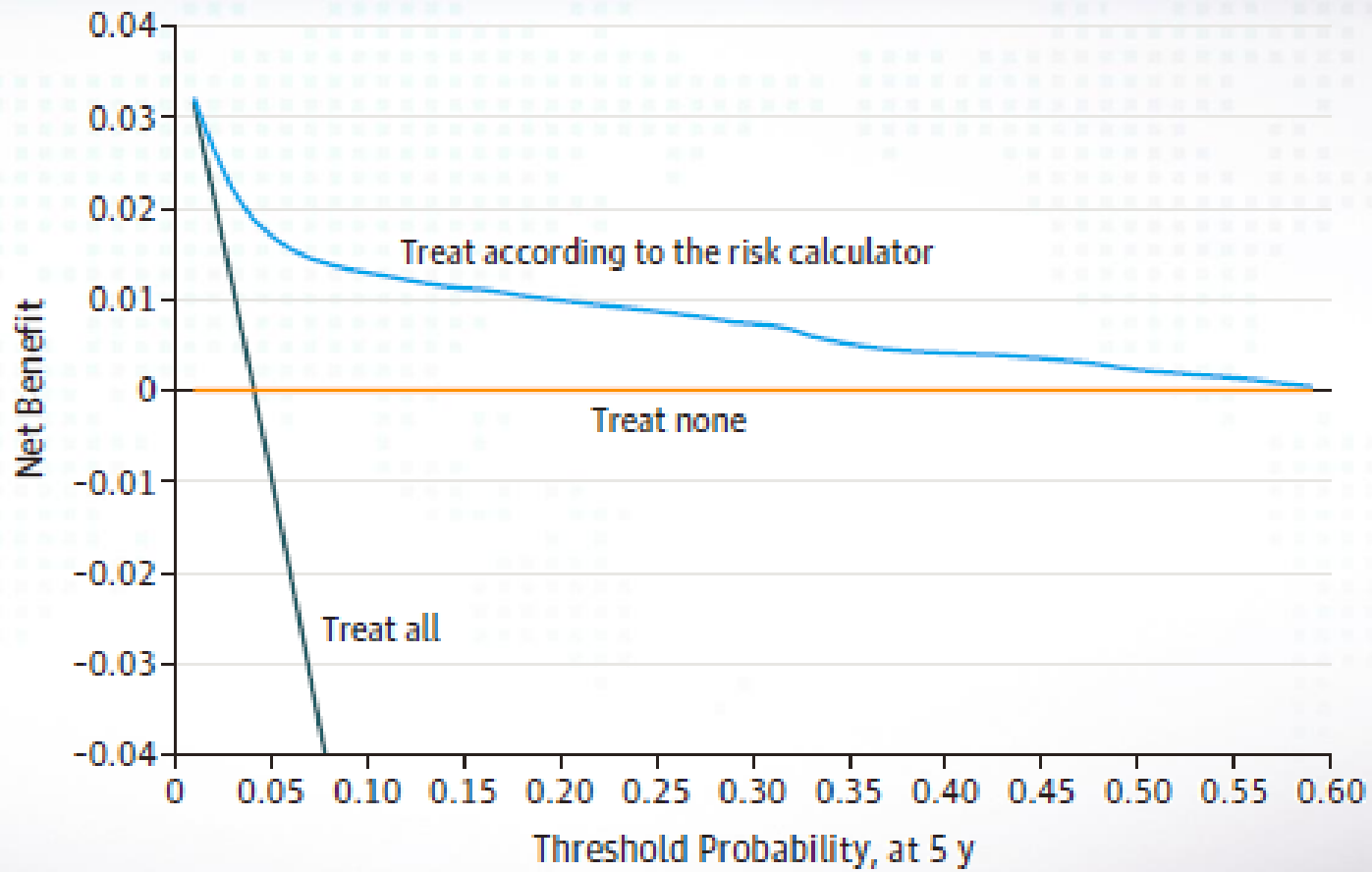
1. Severity of baseline symptoms
2. High negative symptoms
3. Basic symptoms
4. Unusual thought content
5. Cognition (baseline/longitudinal)
6. Social impairment
7. Neuroimaging
8. Electrophysiology
9. Family history of schizophrenia

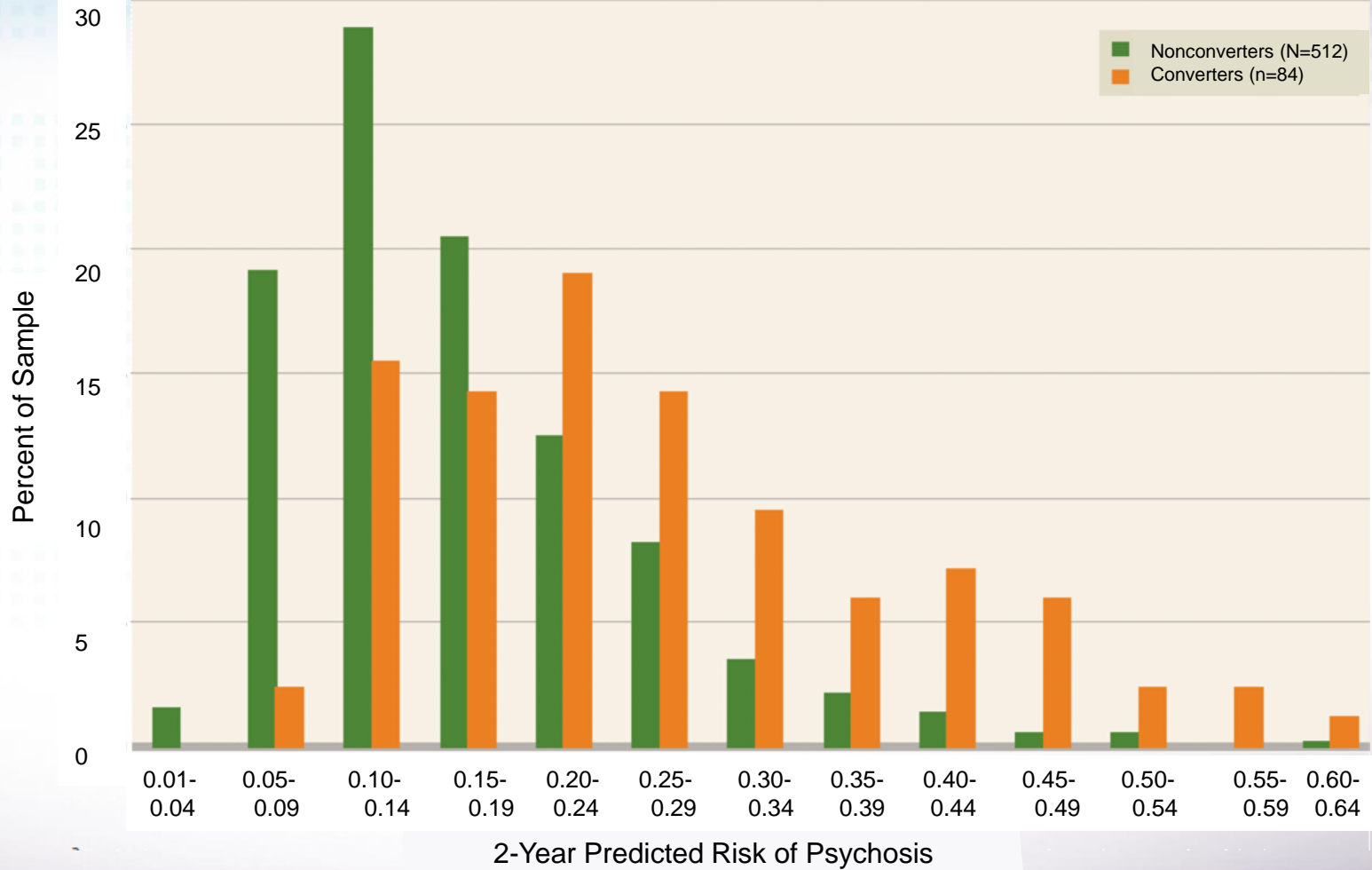


# Prediction Calculators

- Cannon TD et al. An individualized risk calculator for research in prodromal psychosis. *Am J Psychiatry*. 2016 Oct 1;173(10):980-988
- Lee TY et al. Can we predict psychosis outside the clinical high-risk state? A systematic review of non-psychotic risk syndromes for mental disorders. *Schizophrenia Bulletin* 2018, 44(2):276-285.







# RCT: Stafford et al, BMJ; Jan. 2013

- 1246 participants
- Approximate one year transition: 7% versus 20%
- 11 trials
- All control groups received treatment





**Absolute effects of treatments for developing psychosis.  
Data are number of participants per 1000 who will transition.**

<b>Population</b>	<b>Intervention</b>	<b>Control</b>
<b>CBT (risk ratio=0.54)</b>		
Very high risk	162	300
High risk	54	100
<b>CBT and risperidone (risk ratio =0.63)</b>		
Very high risk	189	300
High risk	63	100
<b>Integrated psychotherapy (risk ratio=0.19)</b>		
Very high risk	57	300
High risk	19	100
<b>Fish oil/omega-3 fatty acids (risk ratio=0.18)</b>		
Very high risk	54	300
High risk	18	100

# Clinical High Risk Therapeutics

- Involve family/other
- Individualized assessment
- Reduce stress
- Reduce social isolation
- Sustain role
- Rx specific problems [e.g., sleep, anxiety]
- Staging model



# Non-pathological Targets

- Compensatory
- Resilience
- Positive psychiatry



# Reasons for New Diagnostic Class

- CHR/APS validated
- Anxiety and mood disorders invalidated
- Need for therapeutic discovery
- Need for staging clinical care
- Advantage of placeholder diagnostic concept

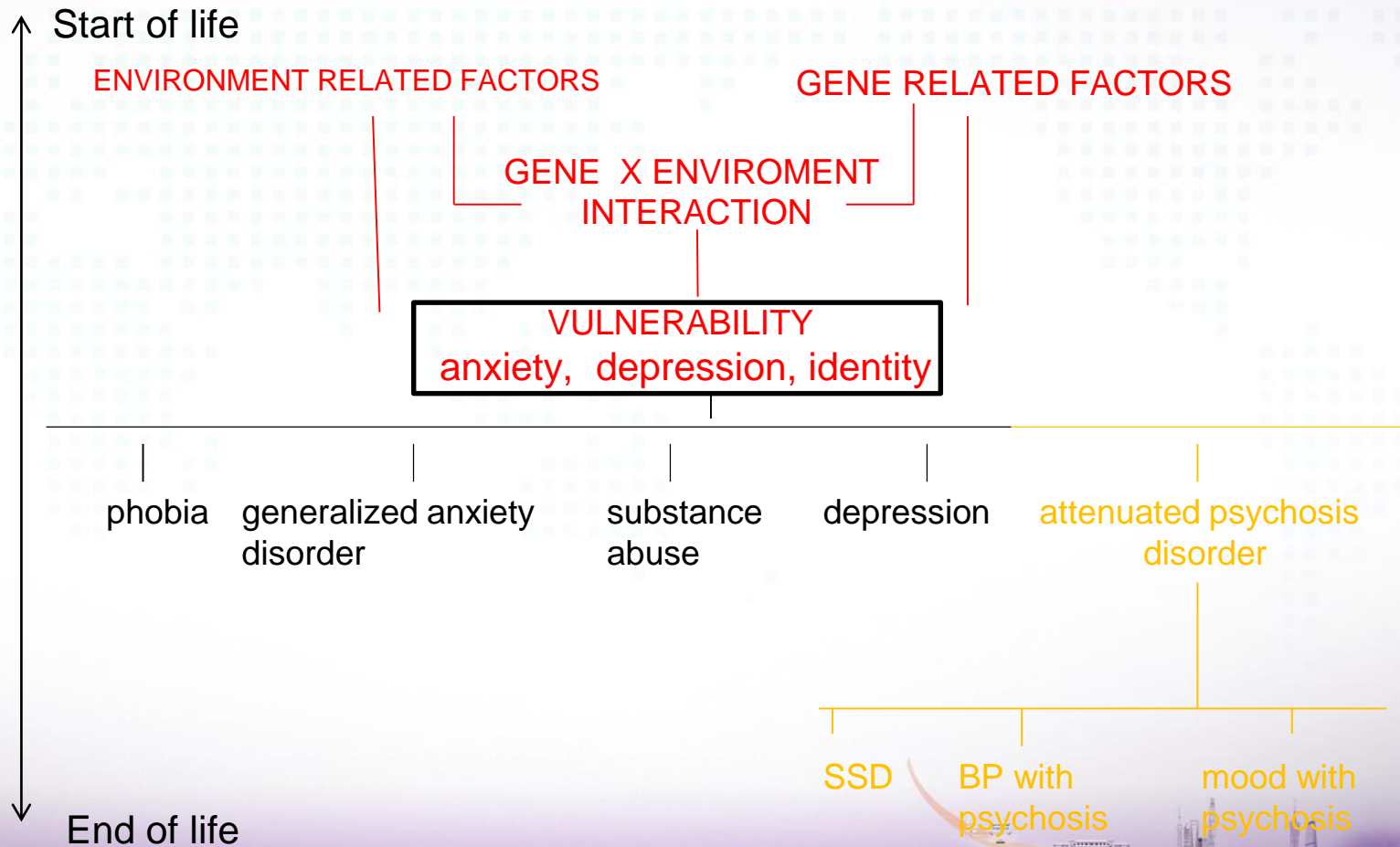


# Competing Paradigms

1. Other disorders with psychosis
2. APS with associated symptoms
3. Extended Psychosis Phenotype



# CONCEPTS OF DISORDER DEVELOPMENT





# Primary Prevention

Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, Leonard S, Stevens KE, Freedman R. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry*, 170(3):290-8, 2013.

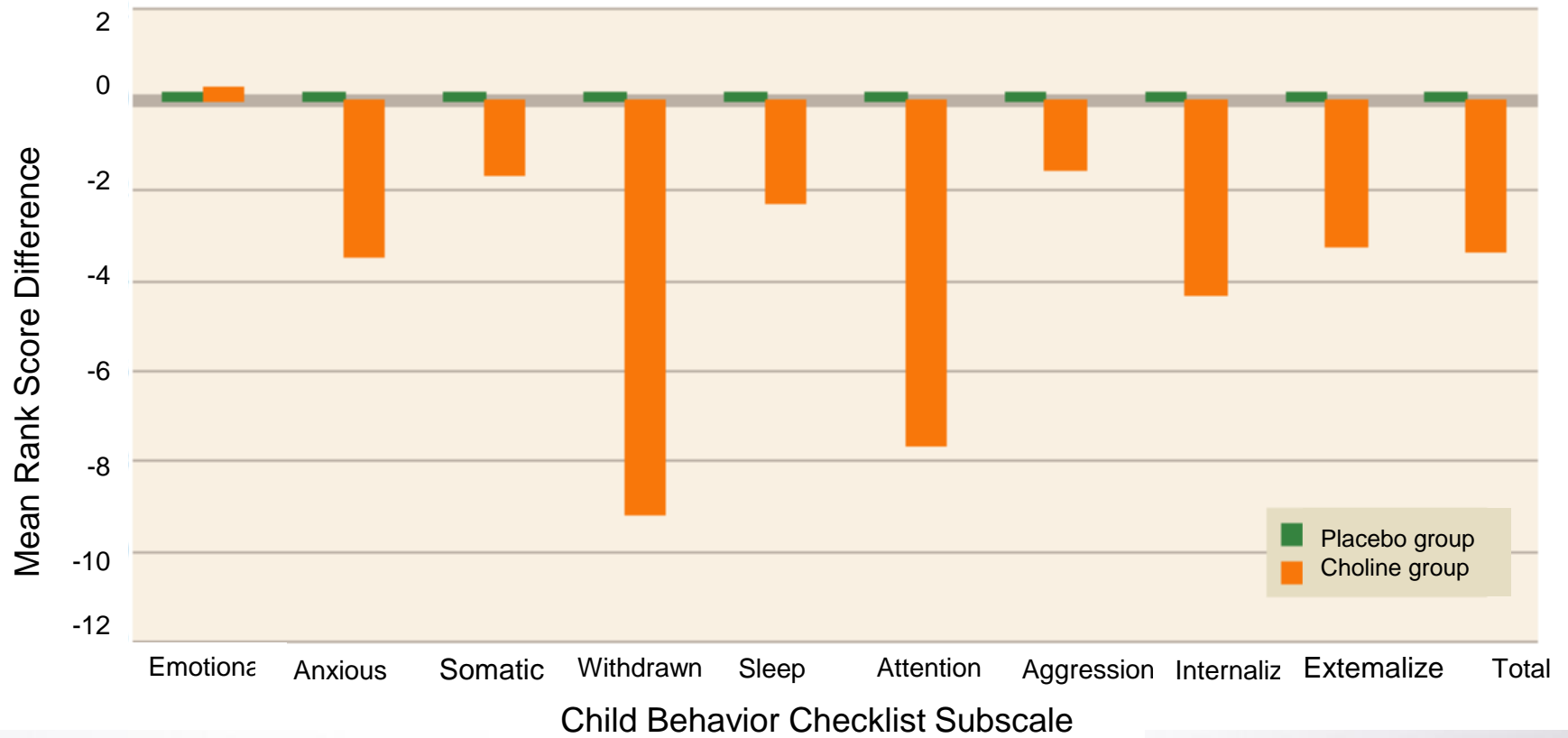
## CONCLUSIONS:

Neonatal developmental delay in inhibition is associated with attentional problems as the child matures. Perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it.

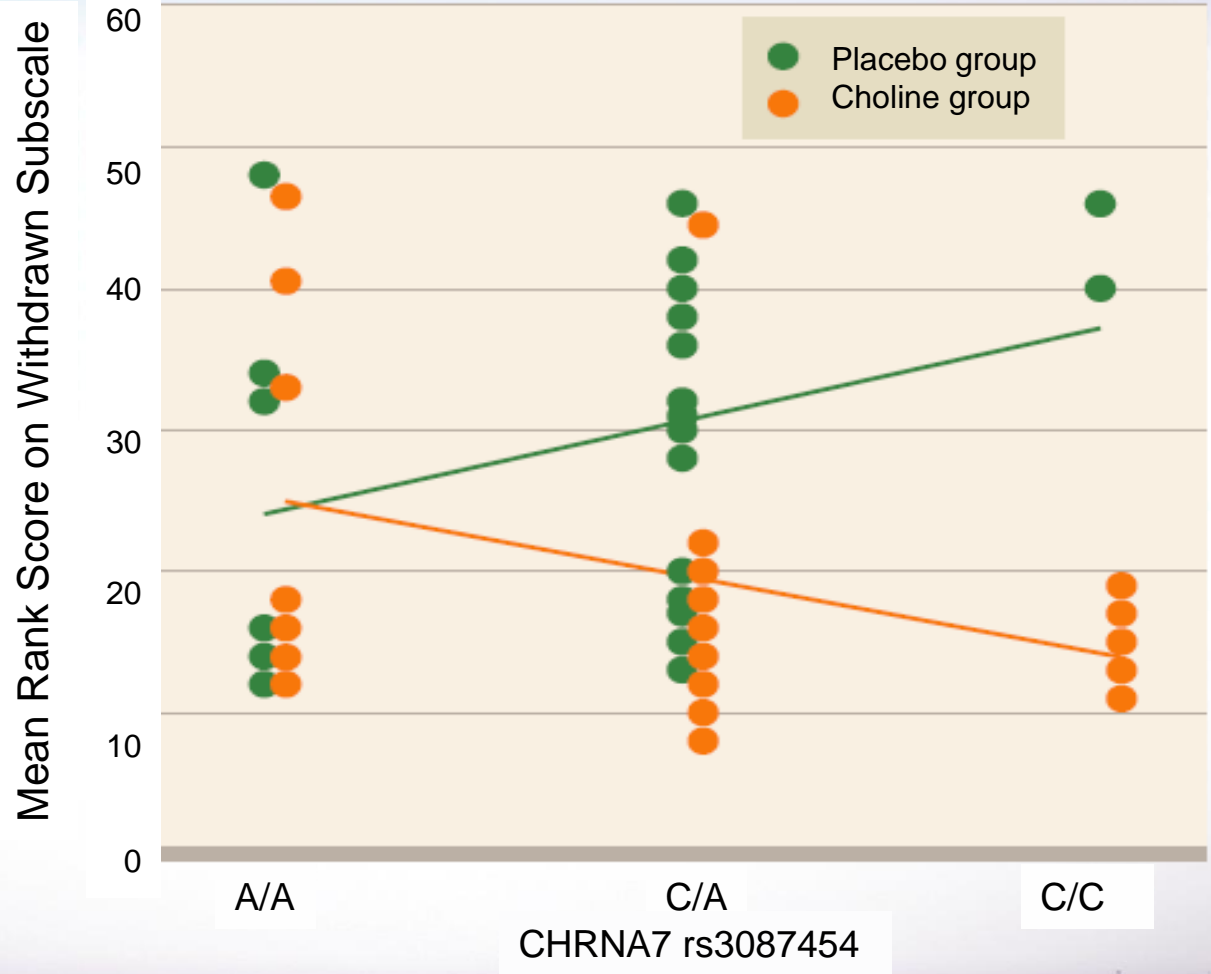
**Comment in:** Rapoport JL. Prevention of schizophrenia: an impossible dream? *Am J Psychiatry* 170(3):245-7, 2013.



### C. Choline Difference From Placebo at 40 Months





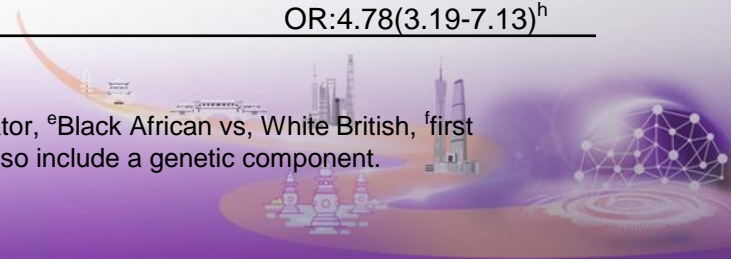


# Primary Prevention of Psychosis

Type of environmental risk factor	Meta-analytical association with psychosis	Association measure type: mean (95% CI)
Parental risk factors	Parental psychosis <sup>29</sup>	RR:7.87(4.14-14.94)
	parental affective disorder <sup>29</sup>	RR:6.42(2.20-18.78)
	Old paternal age <sup>30</sup>	RR:2.22(1.46-3.37) <sup>a</sup>
Perinatal risk factors	Complications of pregnancy <sup>31-33</sup>	OR:2.44(1.13-5.26) <sup>b</sup>
	Abnormal foetal growth and development <sup>31-32</sup>	OR:3.89(1.40-10.84) <sup>c</sup>
	Complications of delivery <sup>31-32</sup>	OR:2.21(1.38-3.54) <sup>d</sup>
	Gestational influenza <sup>33</sup>	RR:1.56(1.05-2.32)
	Season of birth <sup>34</sup>	OR:1.07(1.05,1.08)
Social risk factors	Ethnic minority <sup>35-37</sup>	RR:4.7(3.3-6.8) <sup>e</sup>
	First and second generation immigrant status <sup>38</sup>	IRR:2.3(2.0-2.7) <sup>f</sup>
	Urbanicity <sup>39</sup>	OR:2.37(2.01-2.81)
Later risk factors	Infections <sup>40-42</sup>	OR:2.70(1.34-4.42) <sup>g</sup>
	traumatic brain injury <sup>43</sup>	OR:1.65(1.17-2.32)
	Vitamin D deficiency <sup>44</sup>	OR2.16(1.32-3.56)
	Daily tobacco use <sup>45</sup>	OR:2.18(1.23-3.85)
	Cannabis heavy abuse <sup>46</sup>	OR:3.90(2.84-5.34)
	Childhood trauma and adversity <sup>47</sup>	OR:2.75(2.17-3.47)
	Adult life events <sup>48</sup>	OR:3.19(2.15-4.75)
	Premorbid IQ <sup>49,50</sup>	OR:4.78(3.19-7.13) <sup>h</sup>

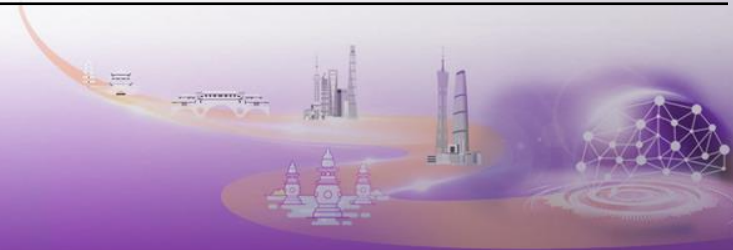
RR - risk ratio, OR - odds ratio, IRR - incidence rate ratio

<sup>a</sup>age >55, <sup>b</sup>gestational age <37 weeks, <sup>c</sup>birth weight <2000g, <sup>d</sup>incubator or resuscitator, <sup>e</sup>Black African vs, White British, <sup>f</sup>first generation migrants, <sup>g</sup>Toxoplasma gondii, <sup>h</sup>IQ<70. Some of these risk factors may also include a genetic component.



# Primary Prevention of Psychosis

Intervention	Supporting evidence	Target
Perinatal phosphatidylcholine	Randomized controlled trial <sup>13</sup>	Electrophysiological biomarkers of neonatal development
School-based interventions	Randomized controlled trials <sup>14,15</sup>	Bullying, victimization, pro-bullying attitudes, pro-victim attitudes, empathy toward victims
Fetal and neonatal N-acetylcysteine	Randomized controlled trials <sup>16</sup>	biomarkers of neuroinflammation and neuroprotection
N-3 polyunsaturated fatty acids	Review <sup>17</sup>	Biomarkers of neuroinflammation
Vitamins A,D,B-group, folic acid	original study, meta-analysis <sup>18,19</sup>	Biomarkers of neuroinflammation
Sulphoraphane	Review <sup>20</sup>	Biomarkers of oxydative stress
Prebiotics	Review <sup>21</sup>	Microbiota dysbiosis
School-based interventions	Randomized controlled trial, review <sup>22,23</sup>	Substance abuse
Exercise training	original studies <sup>24-27</sup>	Brain plasticity, structure, connectivity, cognitive functioning



# Prevention Targets

- Gestational stressors
- Perinatal complications
- Urban
- Childhood neglect/mistreatment
- Developmental abuse [physical, sexual, emotional]
- Toxoplasmosis gondii
- Gliadin positive AB
- Polygenic risk scores [resilience training]



# SUMMARY

- Primary Prevention of vulnerability
- Treat disorder at vulnerability stage
- Secondary Prevention of psychosis
- Tertiary Prevention of functional decline
- Reduce time of untreated pathology



# Near Future

- Animal models that predict human Rx efficacy
- Biobehavioral types that predict Rx efficacy
- Predictor tools for psychosis risk in CHR
- Regulatory acceptance of CHR as disorder
- Pharmaceutical interest in Wellness discovery



# Background Reading

- Fusar-Poli P, Carpenter WT, Woods SW, McGlashan, TH. Attenuated Psychosis Syndrome: Ready for DSM-5.1? *Annu Rev Clin Psychol* 2014 Mar 28;10:155-92
- Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013 Jan;70(1):107-20.
- Cannon T. , Changhong Y, Addington A. et al. An individualized risk calculator for research in prodromal psychosis. *American Journal of Psychiatry*, 2016; 173(10):980-988.
- Fusar-Poli P. Extending the benefits of indicated prevention to improve outcomes of first-episode psychosis. *JAMA Psychiatry* 2017; 74(7):667-668.
- Fusar-Poli P, Rutigliano G, Stahl D, et al. Development and validation of a clinically based risk calculator for the transdiagnostic prediction of psychosis. [published online March 29, 2017] *JAMA Psychiatry* 2017.

