MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Can we prevent schizophrenia?

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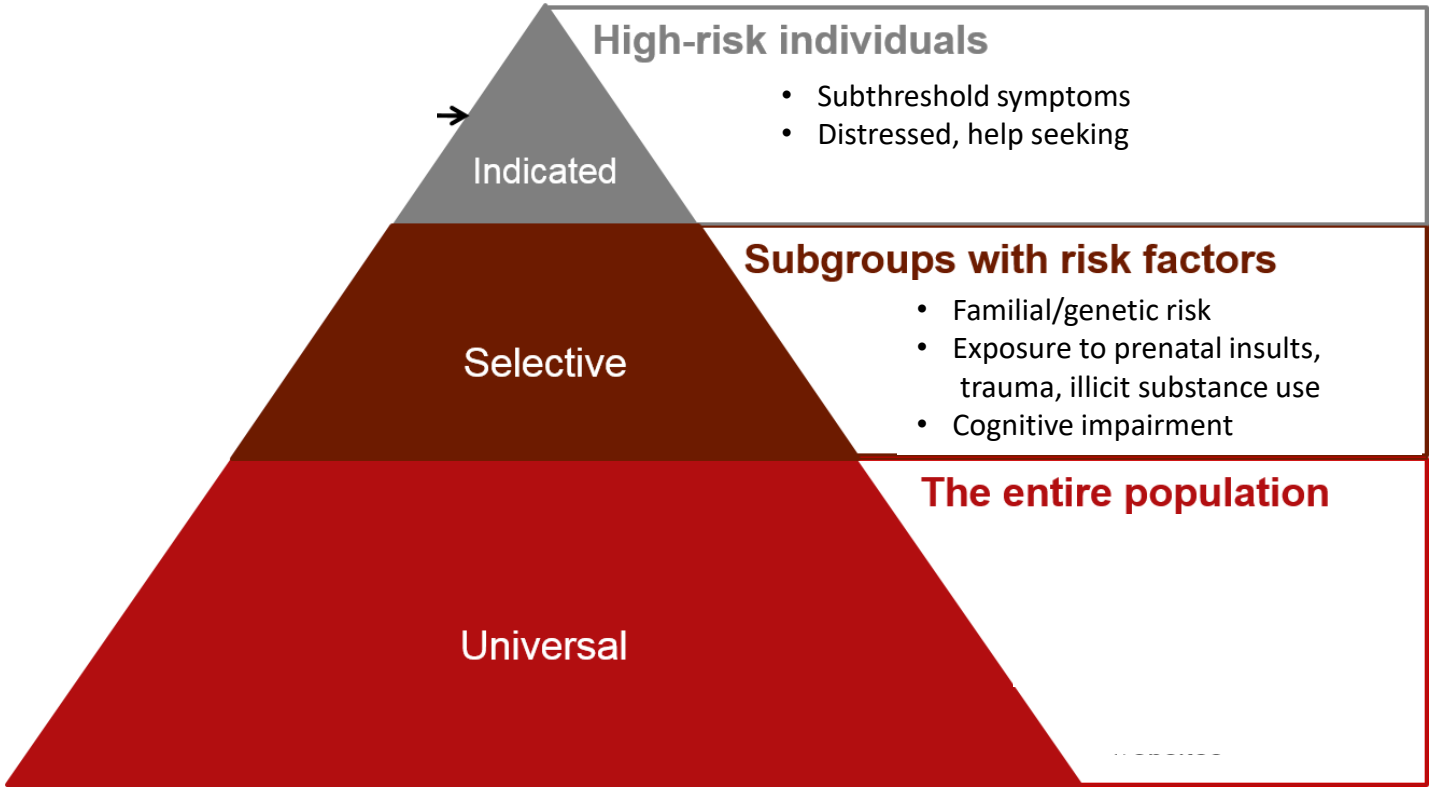
Disclosures

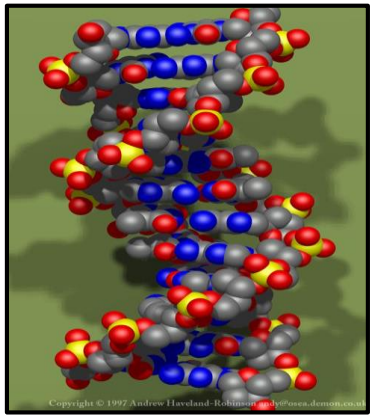
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Prevention in Psychiatry: how does it work?

Categories of risk and preventive interventions:



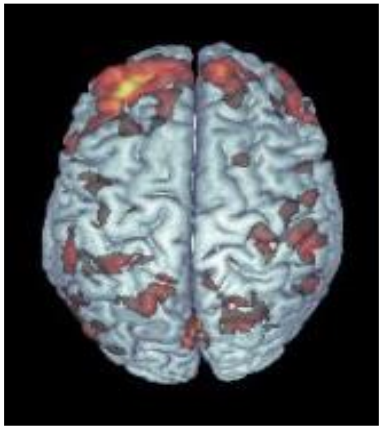
Modifiable and Non-Modifiable Risk Factors



GENES

PAST EXPERIENCES

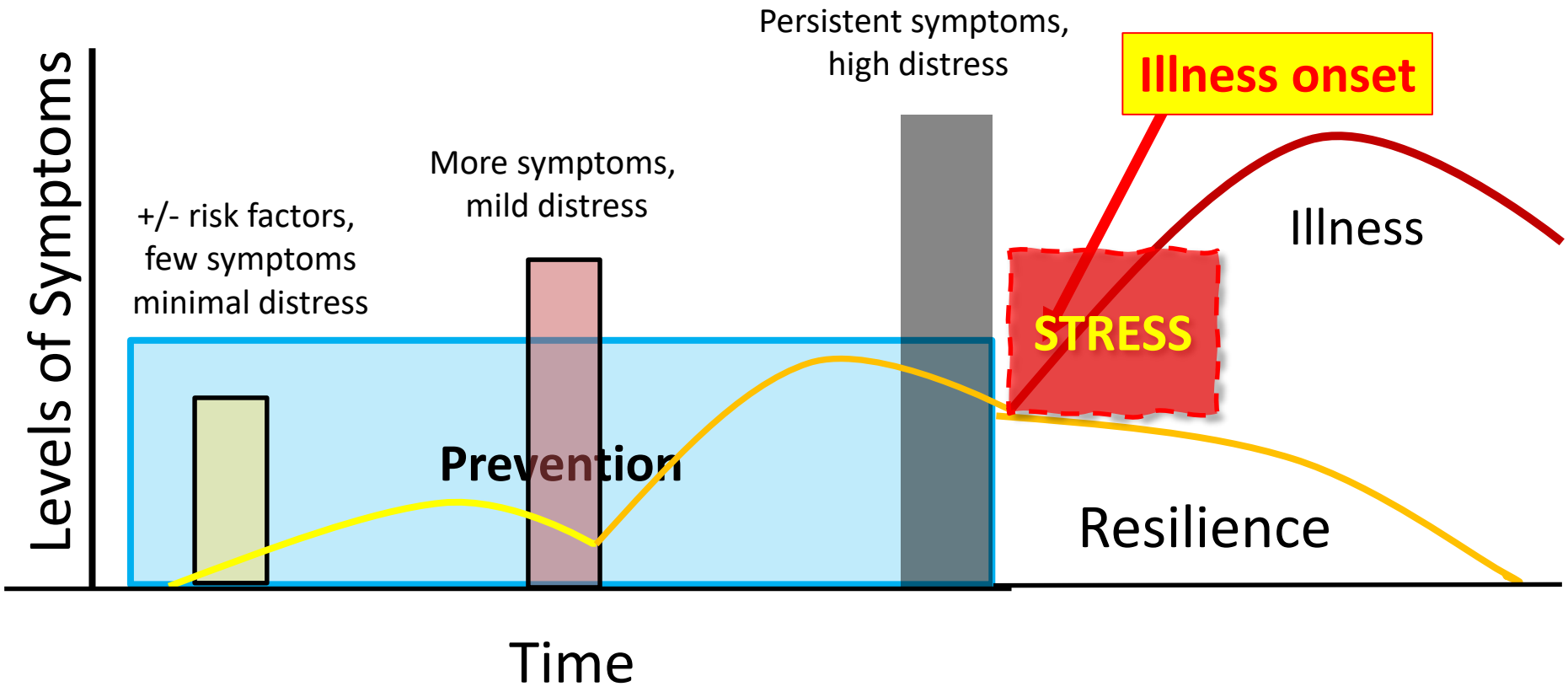
e.g., difficulties in childhood, such as loss of a parent, abuse, neglect



BRAIN CHARACTERISTICS

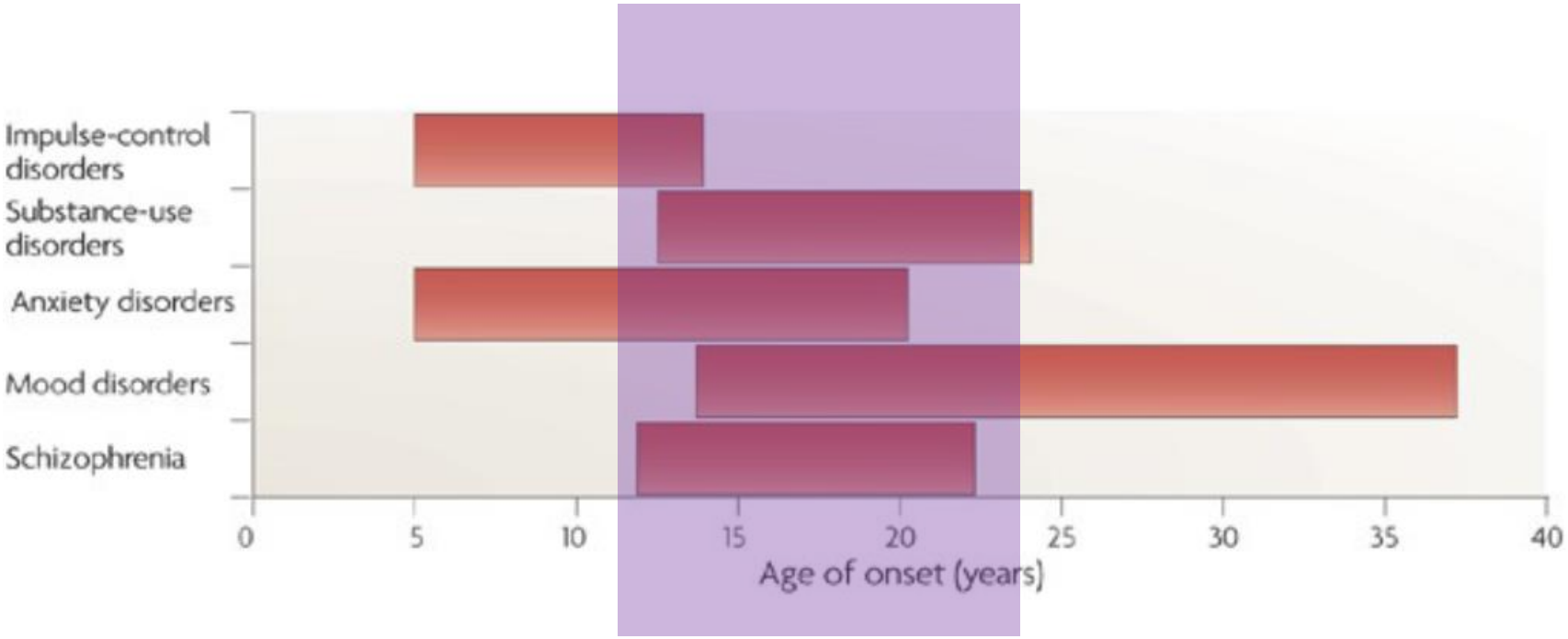
PATTERNS OF THOUGHT

When during the illness trajectory can we intervene?



When during development should we intervene?

Adolescence/young adulthood is a time of life when many mental illnesses emerge for the first time

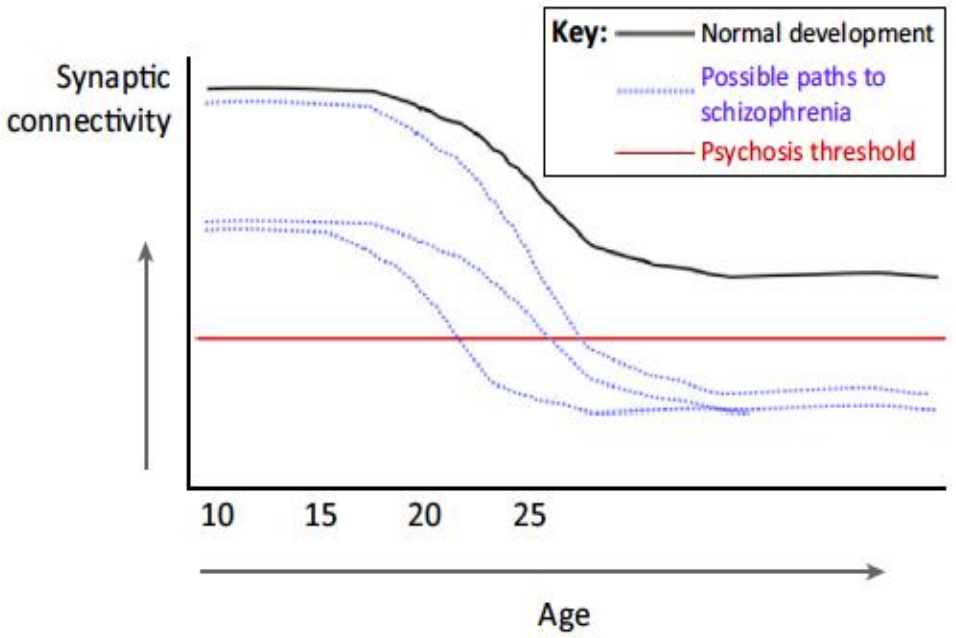


Paus, Keshevan and Geid, Nat Rev Neurosci 2008

When during development should we intervene?

Why is there an increased vulnerability to developing a mental illness during late adolescence & early adulthood?

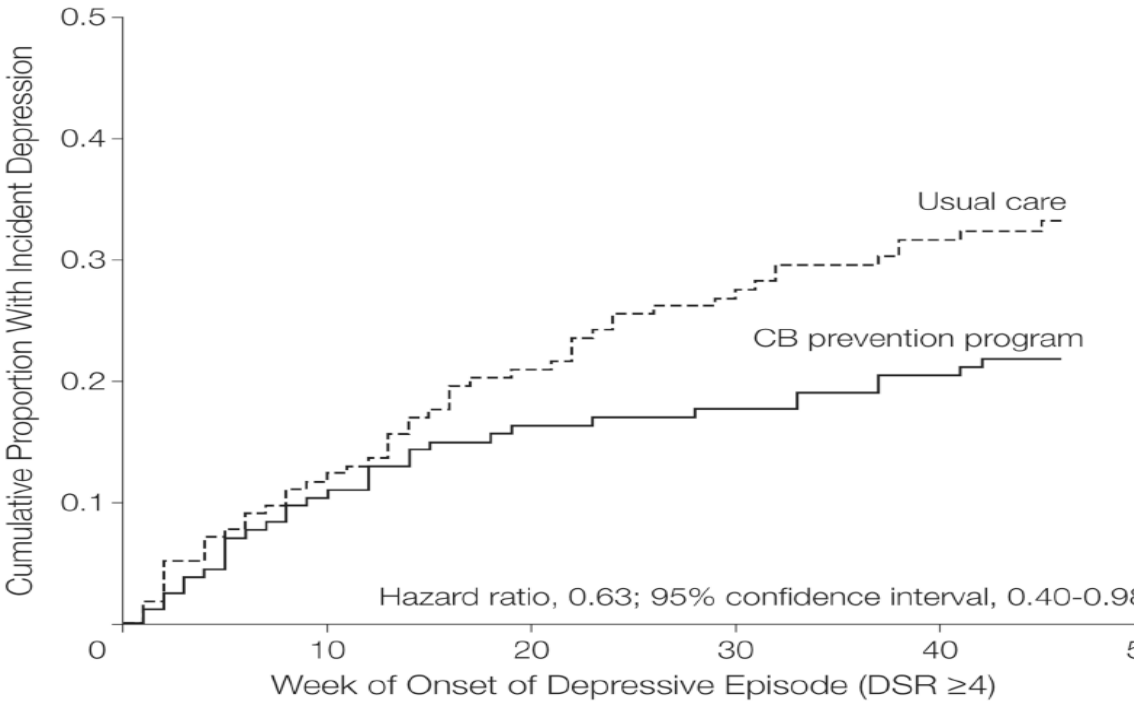
- may be due to a greater sensitivity of the brain to the effects of hormonal changes and stress
- or an acceleration of the loss of synapses that normally occurs during this period



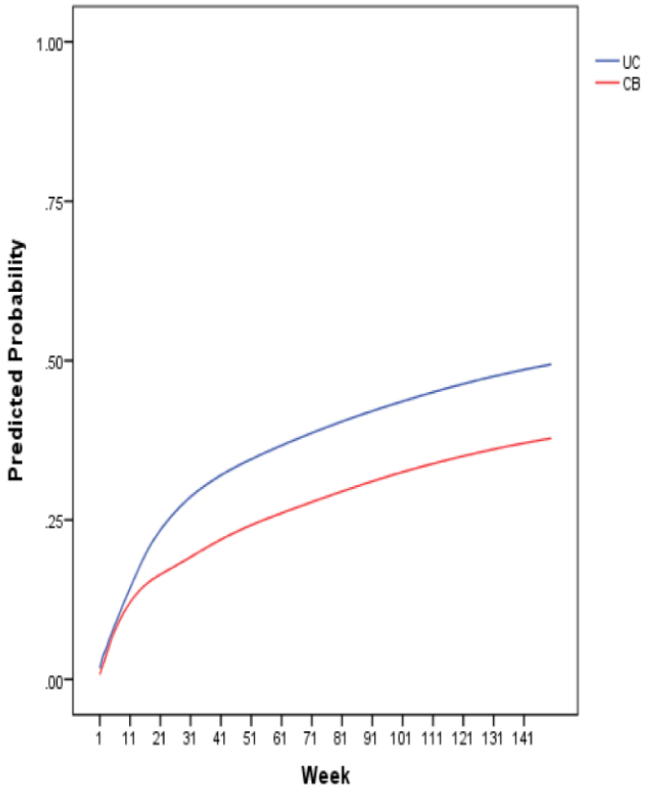
Cannon, TICS 2015

Can any psychiatric disorder be prevented?

Example: Depression



Garber et al, JAMA 2009



Beardslee et al, JAMA Psych 2013

Meta-analyses of depression prevention studies

- A meta-analysis of 32 RCTs of psychological interventions (mainly CBT, group or individual) found **a 21% reduction** in incidence of depression compared to the control group (Van Zoonen et al, 2014)

- A meta-analysis of 8 studies of the efficacy of exercise in preventing depressive symptoms also demonstrated positive effects (Hu et al, 2020)

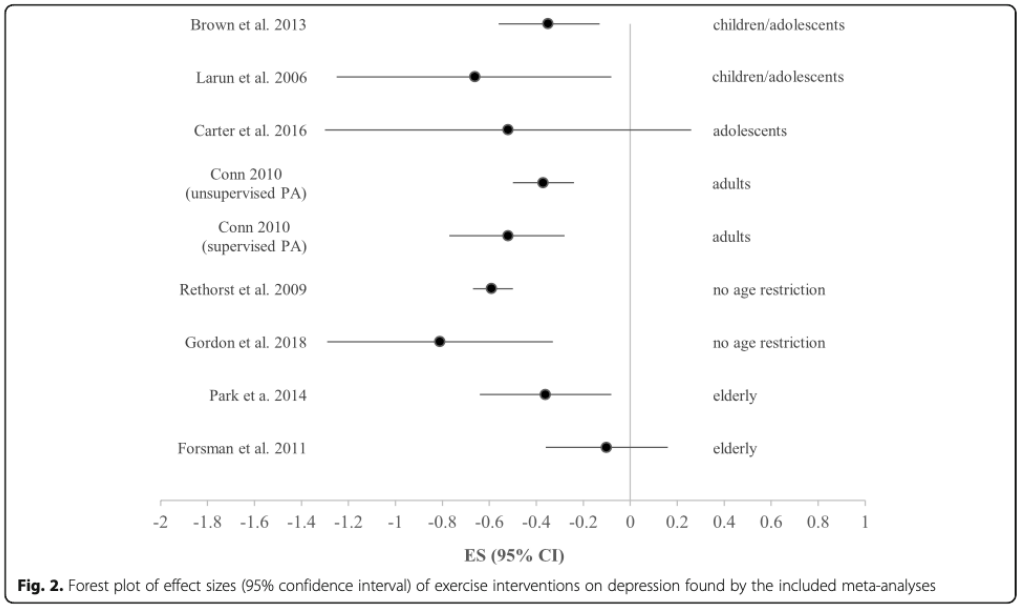


Fig. 2. Forest plot of effect sizes (95% confidence interval) of exercise interventions on depression found by the included meta-analyses

What about schizophrenia?

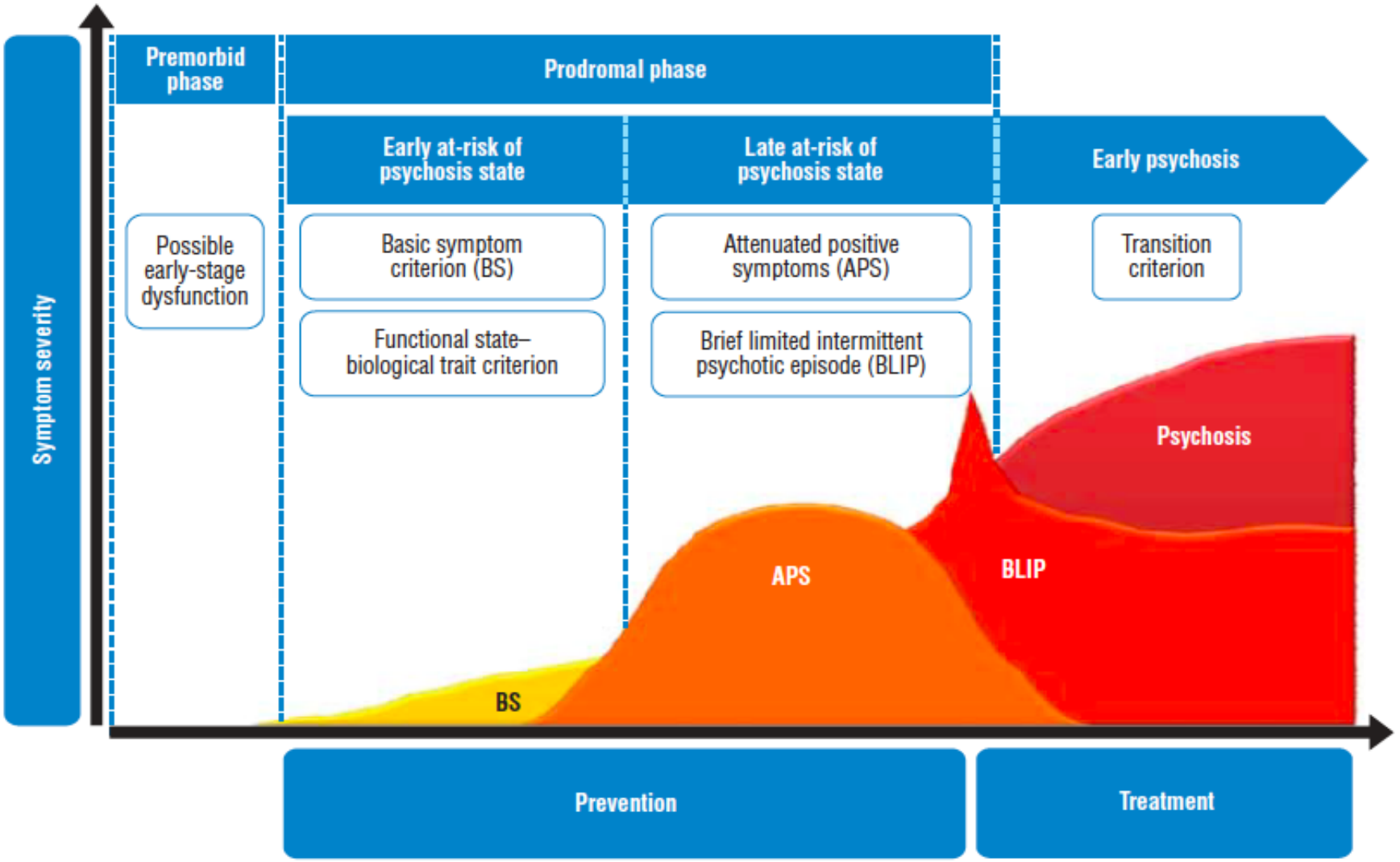
Interventions most often tested to date (during the past 2 decades) for their ability to prevent the onset of psychosis:

- Antipsychotic medication
- Cognitive behavioral therapy (CBT) and related psychotherapies
- Nutritional supplements, most commonly omega-3-fatty acids (fish oil)

- Target risk group: individuals with subsyndromal psychotic symptoms
  - "Ultra-High Risk" (UHR) or "Clinical High Risk" (CHR)

fish oil supplements

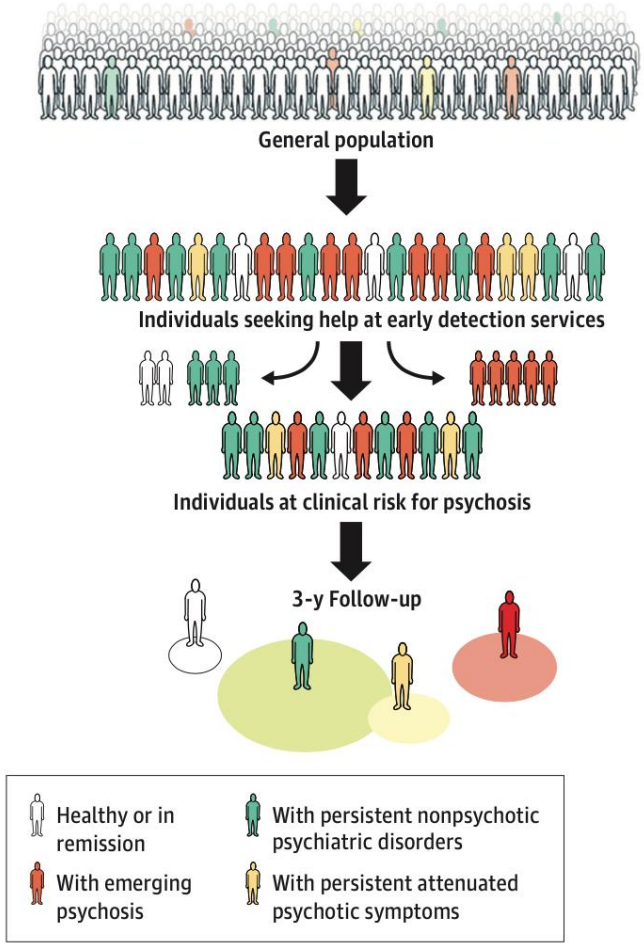
Phases of psychosis risk



Fusar-Poli, JAMA Psych 2013

What is CHR and UHR?

- These are virtually identical research designations of clinical risk for psychosis (based on the presence of subclinical positive symptoms), measured using 2 highly overlapping scales
  - Clinical High Risk (**CHR**) for psychosis, assessed using the *Structured Interview for Prodromal Symptoms (SIPS)* (Miller et al, 1999)
  - Ultra High Risk (**UHR**) for psychosis, assessed using the *Comprehensive Assessment of At-Risk Mental States (CAARMS)* (Yung et al, 2005)



Fusar-Poli et al, JAMA Psych 2020

What is the risk of developing psychosis for these at-risk individuals?

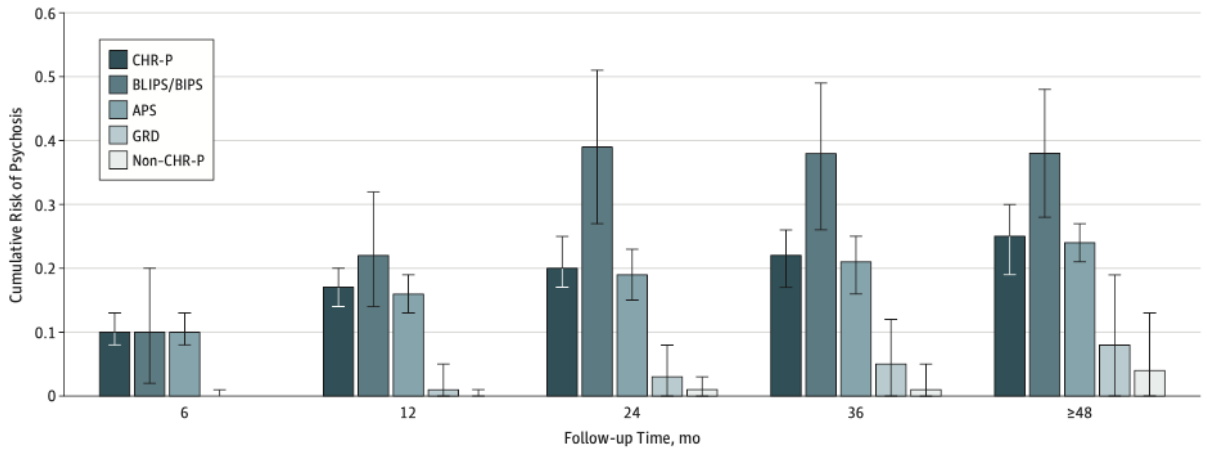
Three categories of UHR/CHR:

1) Attenuated Psychosis Syndrome (APS) or Attenuated Positive Symptom Syndrome (APSS)

2) Brief Limited Intermittent Psychotic Symptoms (BLIPS) or Brief Intermittent Psychotic Syndrome (BIPS)

3) Genetic Risk and Deterioration syndrome (GRD)

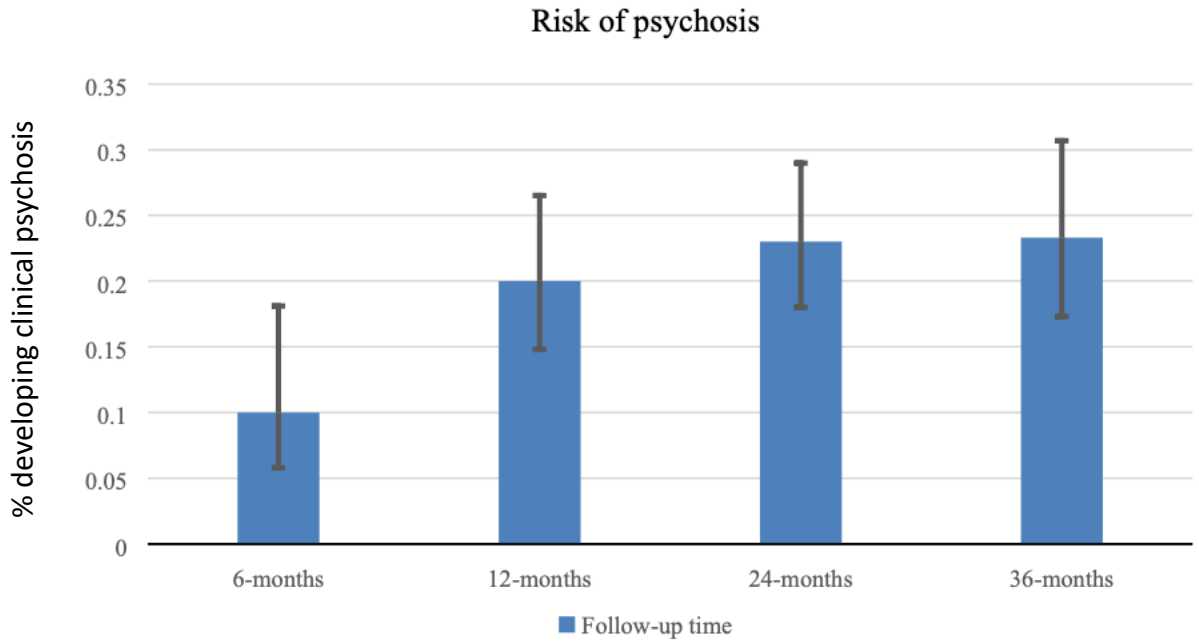
Figure 4. Cumulative Risk of Developing Psychosis in Individuals at Clinical High Risk for Psychosis (CHR-P)



Fusar-Poli et al, JAMA Psych 2020

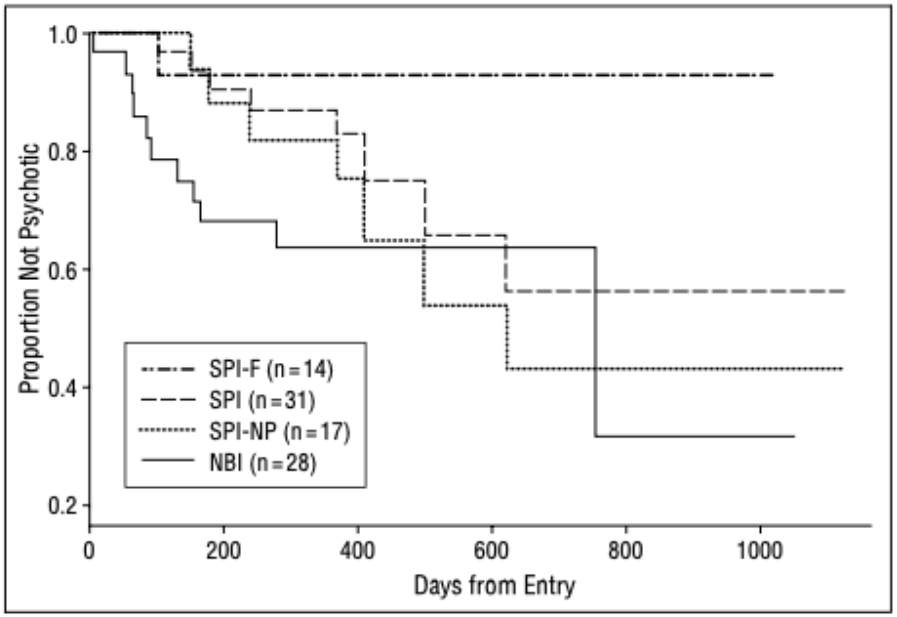
What about in adolescents?

In 4,667 CHR/UHR adolescents (age 12-18, mean 15.6 years):

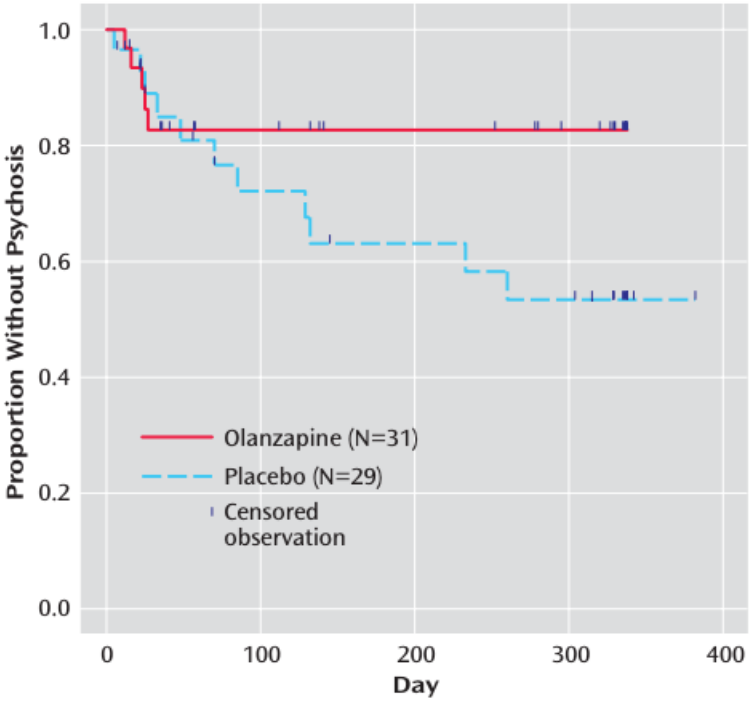


Catalan et al, J Child Psychology and Psychiatry 2020

Can antipsychotic medication prevent psychosis?



McGorry et al, Arch Gen Psych 2002



McGlashan et al, Am J Psych 2006

Initially seemed promising, but subsequent trials and longer follow-up periods have shown that antipsychotics are <u>not effective</u> in preventing the onset of psychotic illness in at-risk individuals (CHR/UHR)

Can Cognitive Behavioral Therapy (CBT) prevent psychosis?

Treatment group	PANSS transition *n* (%)	Antipsychotic medication *n* (%)	DSM–IV psychosis diagnosis *n* (%)
Cognitive therapy	2 (6)	2 (6)	2 (6)
Monitoring	5 (22)	7 (30)	6 (26)

PANSS, Positive and Negative Syndrome Scale.

Morrison et al, Br J Psych 2004

But three years later…

Treatment Group	Follow-up Rate, *N* (%)	PANSS Transition, *N* (%)	Antipsychotic Medication, *N* (%)	*DSM-IV* Psychotic Diagnosis, *N* (%)
Cognitive therapy (*N* = 35)	17 (49)	7 (20)	5 (14)	7 (20)
Monitoring (*N* = 23)	10 (43)	5 (22)	8 (35)	7 (30)

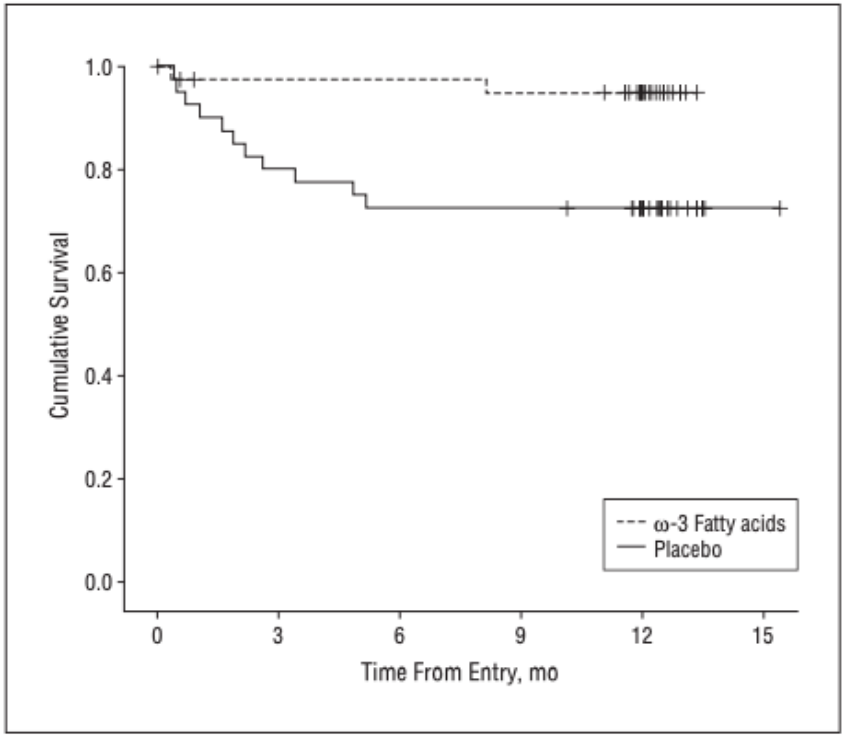
Morrison et al, Schiz Bull 2007

A larger, multi-site trial…

	Month of assessment											
Group	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
Monitoring (cumulative total)	1	2 (3)	0 (3)	2 (5)	1 (6)	0 (6)	3 (9)	1 (10)	0 (10)	1 (11)	1 (12)	1 (13)
Cognitive therapy (cumulative total)	2	1 (3)	1 (4)	1 (5)	1 (6)	0 (6)	1 (7)	0 (7)	0 (7)	1 (8)	0 (8)	2 (10)
Maximum No	288	288	288	288	288	288	288	288	251	224	195	164

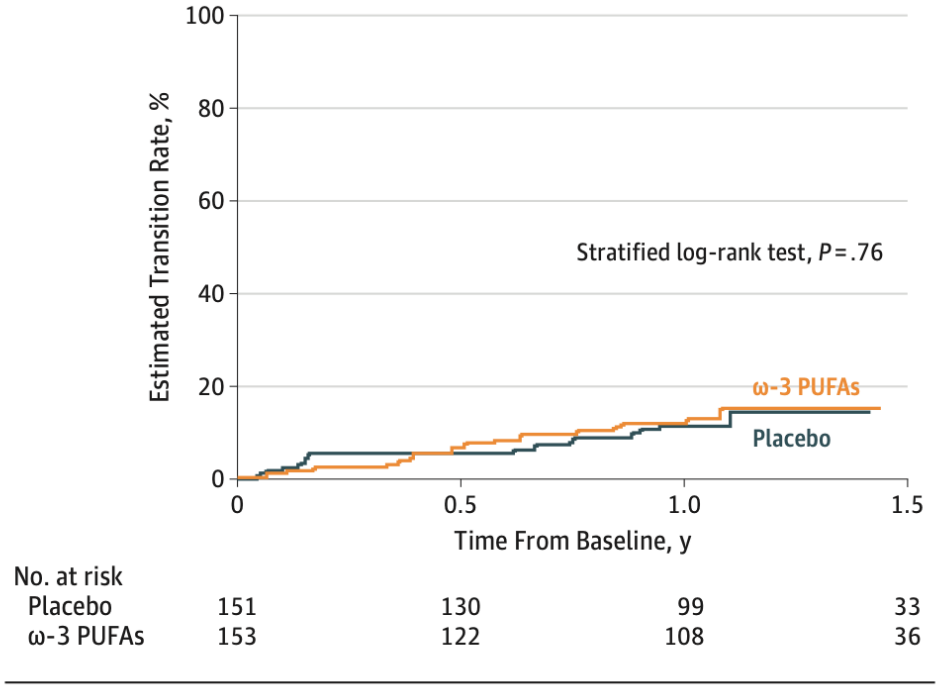
Morrison et al, BMJ 2012

Can Omega-3-Fatty Acids prevent psychosis?



Amminger et al, Arch Gen Psych 2010

the NEURAPRO trial



McGorry et al, JAMA Psych 2017

However, in NEURAPRO, higher baseline levels of, or greater increases in, omega-3-fatty acids predicted greater clinical improvement (Amminger et al, Biol Psych 2019)

Inconsistent results and findings of different meta-analyses

Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis

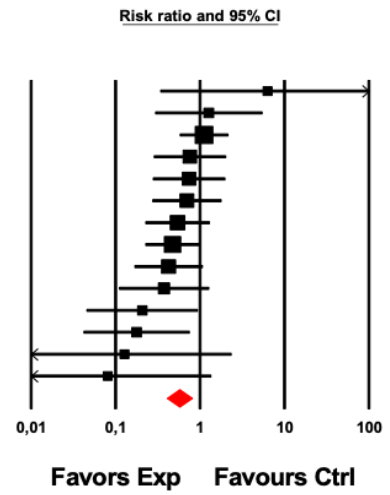
Cathy Davies[1], Andrea Cipriani[2], John P.A. Ioannidis[3-7], Joaquim Radua[1,8,9], Daniel Stahl[10], Umberto Provenzani[1,11], Philip McGuire[12,13], Paolo Fusar-Poli[1,11,13,14]

Davies et al, World Psychiatry 2018; also see Davies et al Front Psych 2018 and Fusar-Poli et al, Front Psych 2019

However, a pooling of studies produced a different result…

Risk Ratios at 12-mont follw-up

	Intervention	Comparison	Time point	Statistics for each study				
				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
DEPTh	CBT	NDRL	12	6,323	0,341	117,088	1,238	0,216
NAPLS	OMEGA	PLAC	12	1,272	0,297	5,454	0,324	0,746
NEURAPRO	OMEGA	PLAC	12	1,119	0,580	2,157	0,334	0,738
RIS-AUS-9ris	RISCBT	ST+PLAC	12	0,760	0,285	2,026	-0,549	0,583
RIS-AUS-9	CBT	ST+PLAC	12	0,742	0,278	1,982	-0,594	0,552
EDIE2-UK	CBT	Mon	12	0,700	0,274	1,788	-0,745	0,456
PACE	RISCBT	NBI	12	0,542	0,226	1,298	-1,374	0,169
EDIE-NL	CBT	EBT	12	0,473	0,226	0,988	-1,993	0,046
PRIME	OLA	PLAC	12	0,425	0,168	1,076	-1,806	0,071
Pozza	CBT	ST	12	0,375	0,110	1,274	-1,572	0,116
EDIE-UK	CBT	Mon	12	0,207	0,046	0,941	-2,039	0,041
Amminger	OMEGA	PLAC	12	0,177	0,042	0,750	-2,350	0,019
ADAPT	CBT	ST	12	0,128	0,007	2,350	-1,385	0,166
EIPS	IPI	ST	12	0,081	0,005	1,352	-1,750	0,080
				0,574	0,408	0,807	-3,194	0,001



Mei et al, Clin Psych Rev, 2021

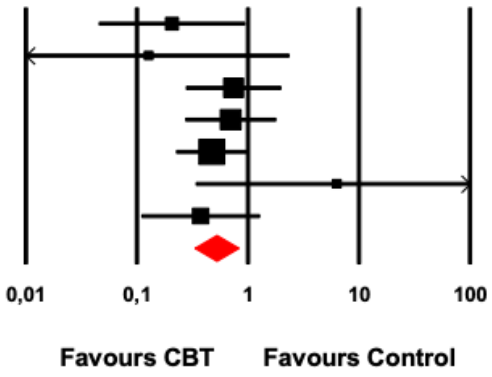
NNT = 16, with the risk of transition to psychosis reduced overall by 43%

- no significant effects on functioning, quality of life

CBT may have a preventive (or delaying) effect

Pooled effects of CBT on transition rate at 12 months

Study name	Intervention	Comparison	Time point	Statistics for each study				
				Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
EDIE-UK	CBT	Mon	12	0,207	0,046	0,941	-2,039	0,041
ADAPT	CBT	ST	12	0,128	0,007	2,350	-1,385	0,166
RIS-AUS-9	CBT	ST+PLAC	12	0,742	0,278	1,982	-0,594	0,552
EDIE2-UK	CBT	Mon	12	0,700	0,274	1,788	-0,745	0,456
EDIE-NL	CBT	EBT	12	0,473	0,226	0,988	-1,993	0,046
DEPTh	CBT	NDRL	12	6,323	0,341	117,088	1,238	0,216
Pozza	CBT	ST	12	0,375	0,110	1,274	-1,572	0,116
				0,523	0,332	0,823	-2,802	0,005



Mei et al, Clin Psych Rev, 2021

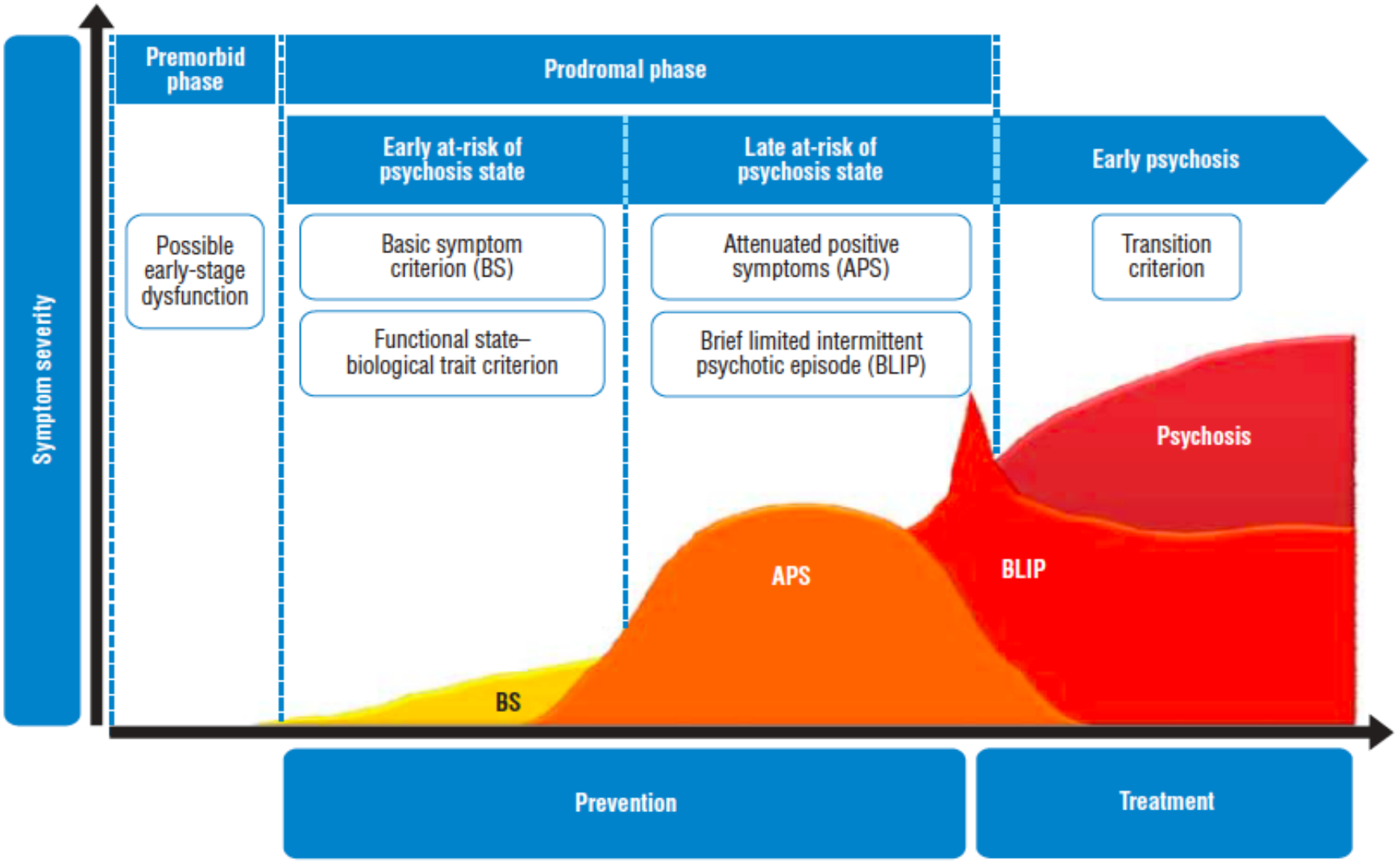
What are the reasons for the weak, inconsistent effects?

- Low transition rates in later studies (perhaps due to a greater amount of community-based recruitment), leading to inadequate power

- Efficacy of the control condition in reducing transition rates, i.e., both groups improved clinically, potentially due to overall improvements in "usual" care for this population

- Heterogeneity within the CHR population: some with more severe, persistent symptoms, others with transient symptoms, potentially linked to different underlying biological mechanisms

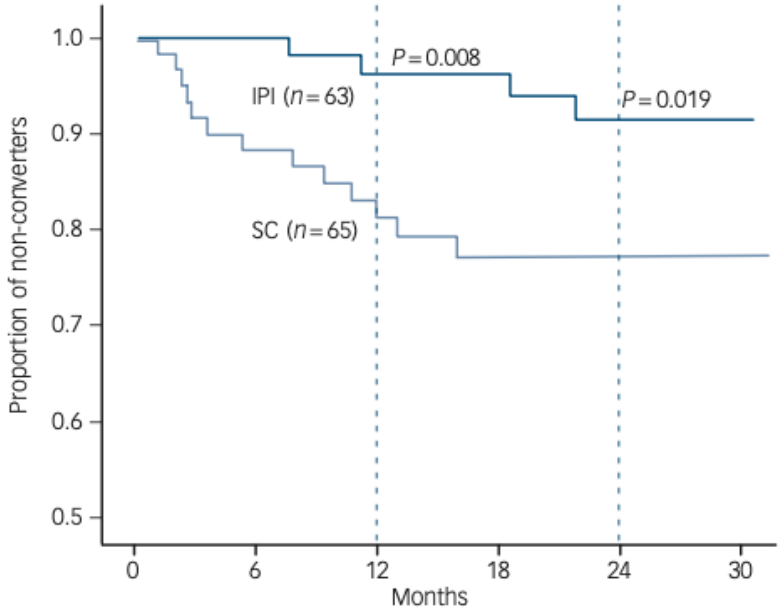
Phases of psychosis risk



Fusar-Poli, JAMA Psych 2013

Earlier target?

- An RCT of an Integrated Psychological Intervention (a combination of family, group and individual treatment, plus cognitive remediation) vs. supportive counseling in individuals with “basic symptoms”– cognitive and perceptual changes, with little disability



Significant effects, requires replication

Bechdolf et al, Br J Psych 2012

“Transdiagnostic” at-risk states

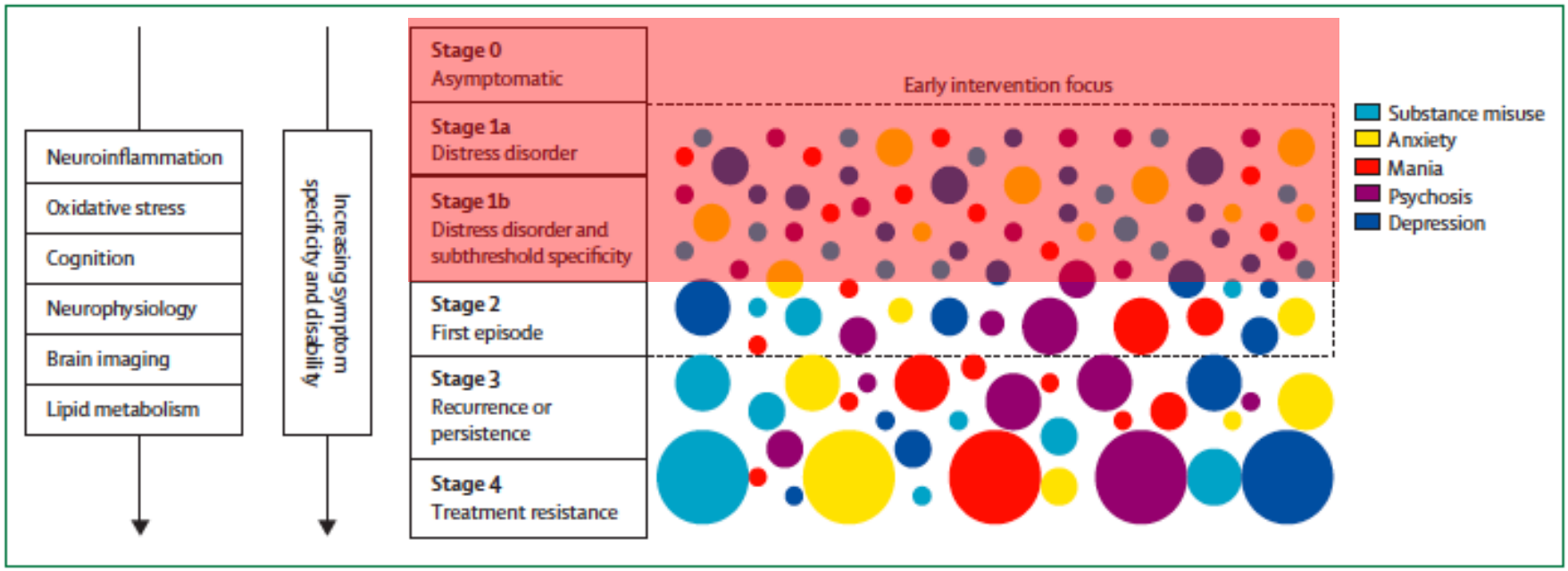


Figure: Biomarkers and clinical staging in psychiatry

Nieman and McGorry, Lancet 2015

Earlier, transdiagnostic target?

- **Psychotic experiences (PEs)** are low-level subclinical psychotic symptoms that are typically benign but increase risk for developing a psychotic disorder 2-6 fold, depending on their severity, persistence and how distressing they are
- People with PEs and/or mild depression received a brief intervention called **Resilience Training (RT)** (Burke et al, 2020) - a 4 session, group-based therapy which focuses on teaching 3 evidence-based skills:

Mindfulness

- Shown to reduce a wide range of mental health symptoms

Self-Compassion

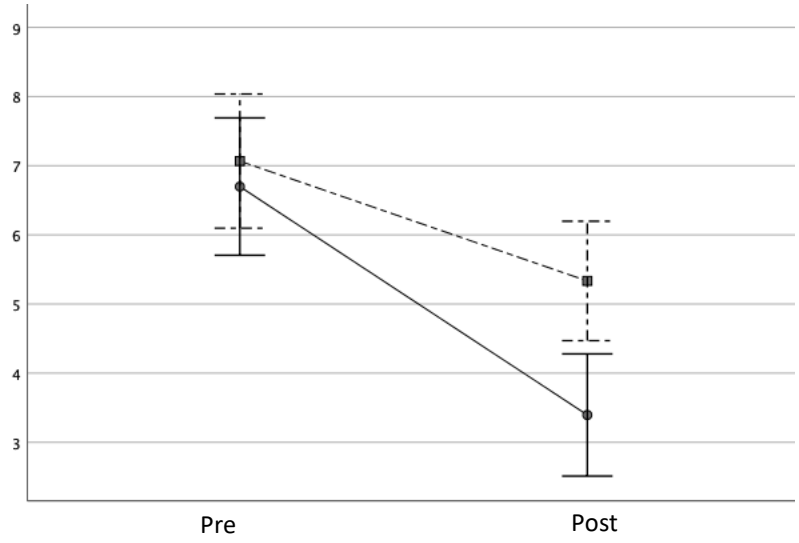
- Shown to lower levels of distress

Mentalization

- Shown to improve social functioning

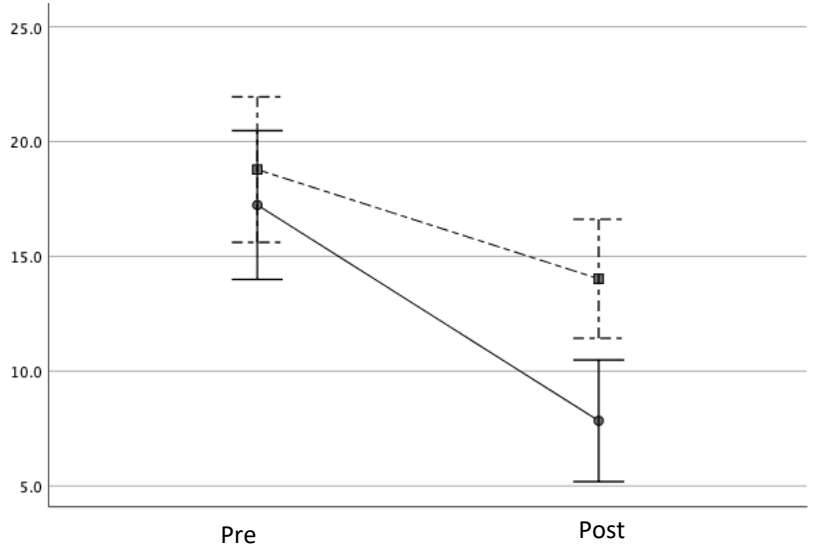
Resilience Training for early stage, transdiagnostic risk

In an RCT, Resilience Training (RT) led to significant decreases in PEs and distress associated with PEs



Total Psychotic Experiences

Group x time interaction:
$F(1,86) = 7.66$, $p = .007$



Distress from Psychotic Experiences

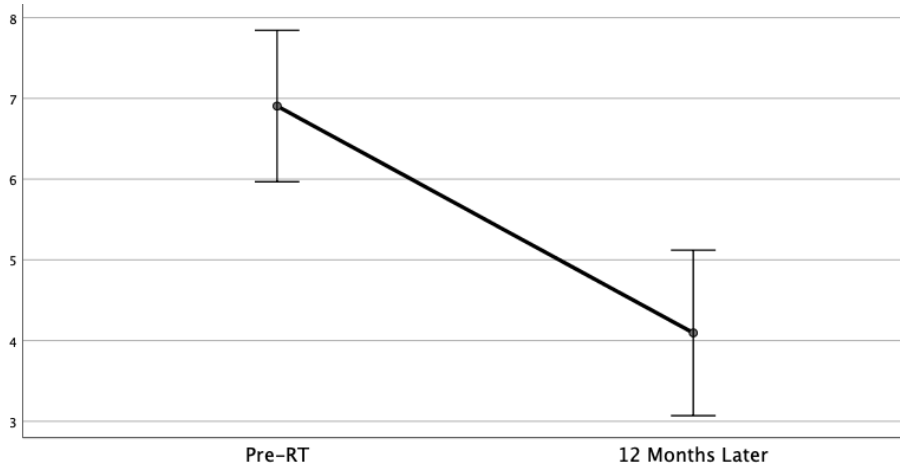
Group x time interaction:
$F(1,86) = 7.46$, $p = .008$

—— Resilience Training (n = 43)

- - - - - Waitlist Control (n = 45)

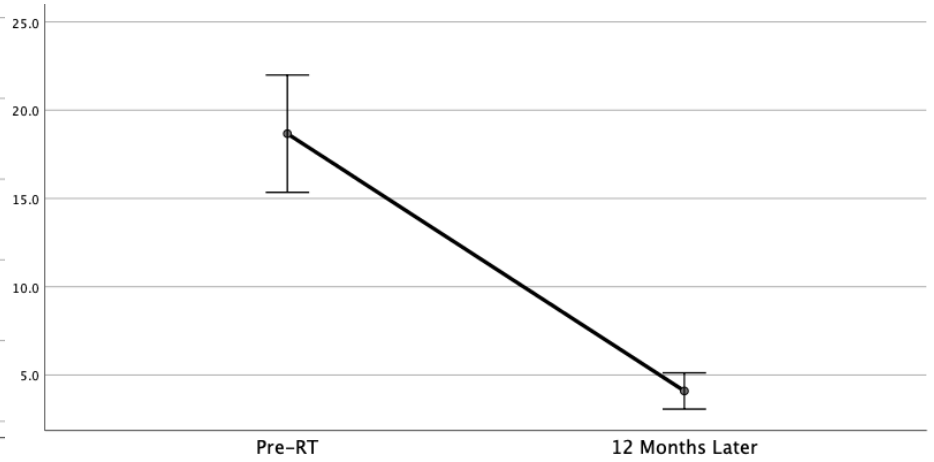
Resilience Training for early stage, transdiagnostic risk

These effects were maintained 12 months later



Total Psychotic Experiences

$t(41) = 5.93$, $p < .001$, $d = -.96$



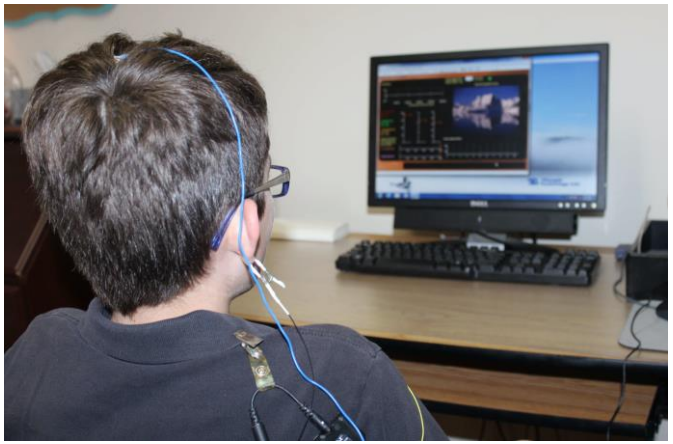
Distress from Psychotic Experiences

$t(41) = 4.53$, $p < .001$, $d = -.79$

Luther, DeTore et al, in preparation

Novel interventions for the prevention of psychosis currently under study

- Mindfulness-based interventions
- Neurocognitive and social cognitive remediation
- Exercise
- Neurofeedback
- Transcranial Direct Current Stimulation
- Antidepressants
- Phosphodiesterase inhibitors
- Oxytocin
- Cannabidiol
- Aspirin
- Minocycline
- N-Acetylcysteine
- Sulforaphane



neurofeedback

Other ways to define psychosis risk

- Risk calculators, machine learning
- Electronic health records
- Polygenic risk score for schizophrenia, other biomarkers

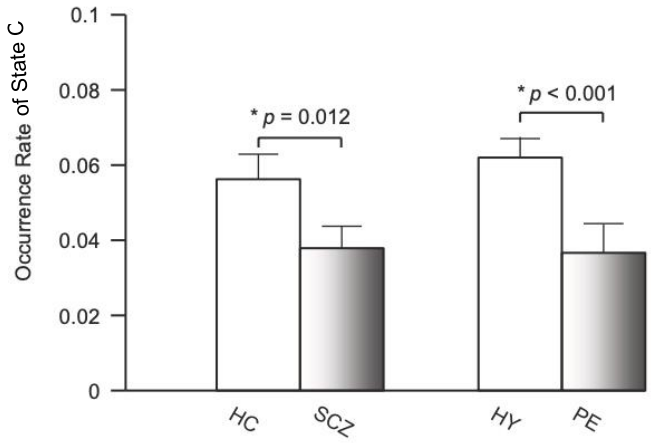
Predictors of conversion to psychosis in 596 CHR participants from the second phase of the North America Prodrome Longitudinal Study (NAPLS 2), elements of a "risk calculator":

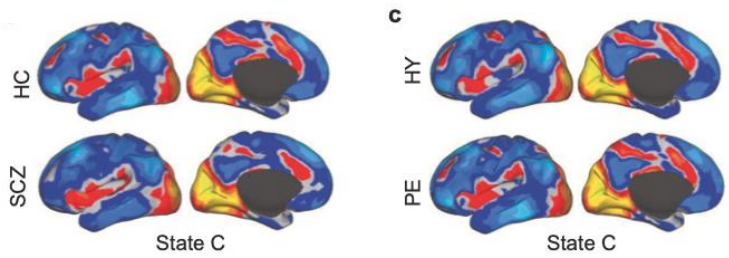
Predictor	Multivariate Model			C-index[a]	
	Hazard Ratio	95% CI	p	Decrement if removed	Increase if added
Modified SIPS P1+P2	2.1	1.6 – 2.7	<0.001	0.092	N/A[b]
Decline in social functioning	1.3	1.1 – 1.5	0.01	0.014	0.015
HVLT Trials 1–3 summed	0.8	0.6 – 0.9	0.05	0.007	0.029
Digit Symbol raw score correct	0.8	0.5 – 1.1	0.10	0.006	0.033
Age	0.7	0.5 – 1.1	0.09	0.004	0.012
Stressful Life Events	1.2	0.9 – 1.6	0.21	0.001	–0.004
Family History of Psychosis	1.2	0.7 – 2.1	0.55	0.000	0.001
Traumas	1.0	0.8 – 1.3	0.99	–0.004	0.002

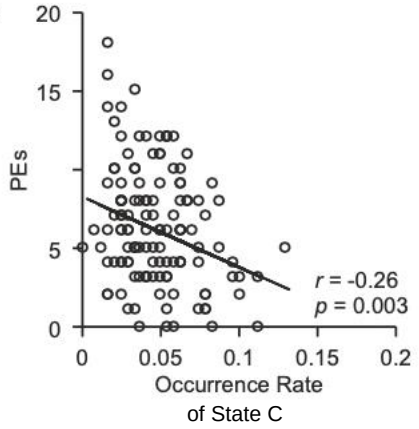
Cannon et al, Am J Psych 2016

One potential biomarker of psychosis

Diminished occurrence of a network “state” (activation of sensory-limbic circuits) is characteristic of schizophrenia AND subsyndromal psychosis (those with psychotic experiences, PEs)







The anatomical distribution of this state is not different among the groups

Wang et al, Mol Psych 2020

HC, healthy controls; SCZ, individuals with schizophrenia;
HY, healthy youth; PE, individuals with psychotic experiences

The Attenuated Psychosis Syndrome

- Recommendations for treatment of patients with the **Attenuated Psychosis Syndrome** (APS, currently listed in the Appendix of DSM-5):
  - Close monitoring of mental status, given elevated psychosis risk, with treatment of co-morbid psychiatric symptoms as indicated (depression, anxiety, substance misuse)
  - Supportive therapy
  - Problem solving focus
  - Consider CBT, omega-3-fatty acids
  - Treatment with antipsychotic medications is not recommended, due to their unfavorable risk-benefit ratio, unless risk of self-harm or aggression is present

Tsuang et al, Schiz Res 2013; Mei et al, Clin Psych Rev 2021

Criteria for APS:

A. At least one of the following symptoms are present in attenuated form with sufficient severity and/or frequency to warrant clinical attention:
   1. delusions/delusional ideas
   2. hallucinations/perceptional abnormalities
   3. disorganized speech/communication

B. Symptoms in Criterion A must be present at least once per week for the past month.

C. Symptoms in Criterion A must have begun or worsened in the past year.

D. Symptoms in Criterion A are sufficiently distressing and disabling to the individual and/or legal guardian to lead them to seek help.

E. Symptoms in Criterion A are not better explained by any other DSM-5 diagnosis, including Substance-Related Disorders.

F. Clinical criteria for a Psychotic Disorder have never been met

Conclusions & Future Directions

- Can we prevent schizophrenia? We don't know yet…

- Advances in ongoing and future research and clinical care:
  - Target both **narrower** (e.g., biomarker-based) and **broader** (early, transdiagnostic) **at-risk states**
  - Use **adaptive** study designs (e.g., SMARTs: Sequential Multiple Assignment Randomized Trials) and treatment algorithms
  - Account for **heterogeneity**, using a precision/personalized medicine approach
  - Focus on a **broader range of outcomes**, in addition to the onset of clinical psychosis, e.g., day-to-day functioning and quality of life, and transition to a range of diagnostic outcomes
  - Incorporate biological or other objective information as targets and outcomes