

Prevention of Psychiatric Illnesses

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October 16, 2026

Disclosures

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

Prevention in medicine – a success story

- **Prenatal vitamins** prevent neural tube defects
- **Vaccinations** prevent childhood and adult infections
- **Smoking cessation** prevents cardiovascular disease, cancer
- **Tests that detect early signs of cancer (e.g., the Pap smear, mammogram, colonoscopy, and PSA test)** prevent serious forms of cancer

What about mental health?

Many studies of preventive approaches for depression, psychosis, anxiety, PTSD, perinatal depression, eating disorders, substance abuse, suicide, among other conditions

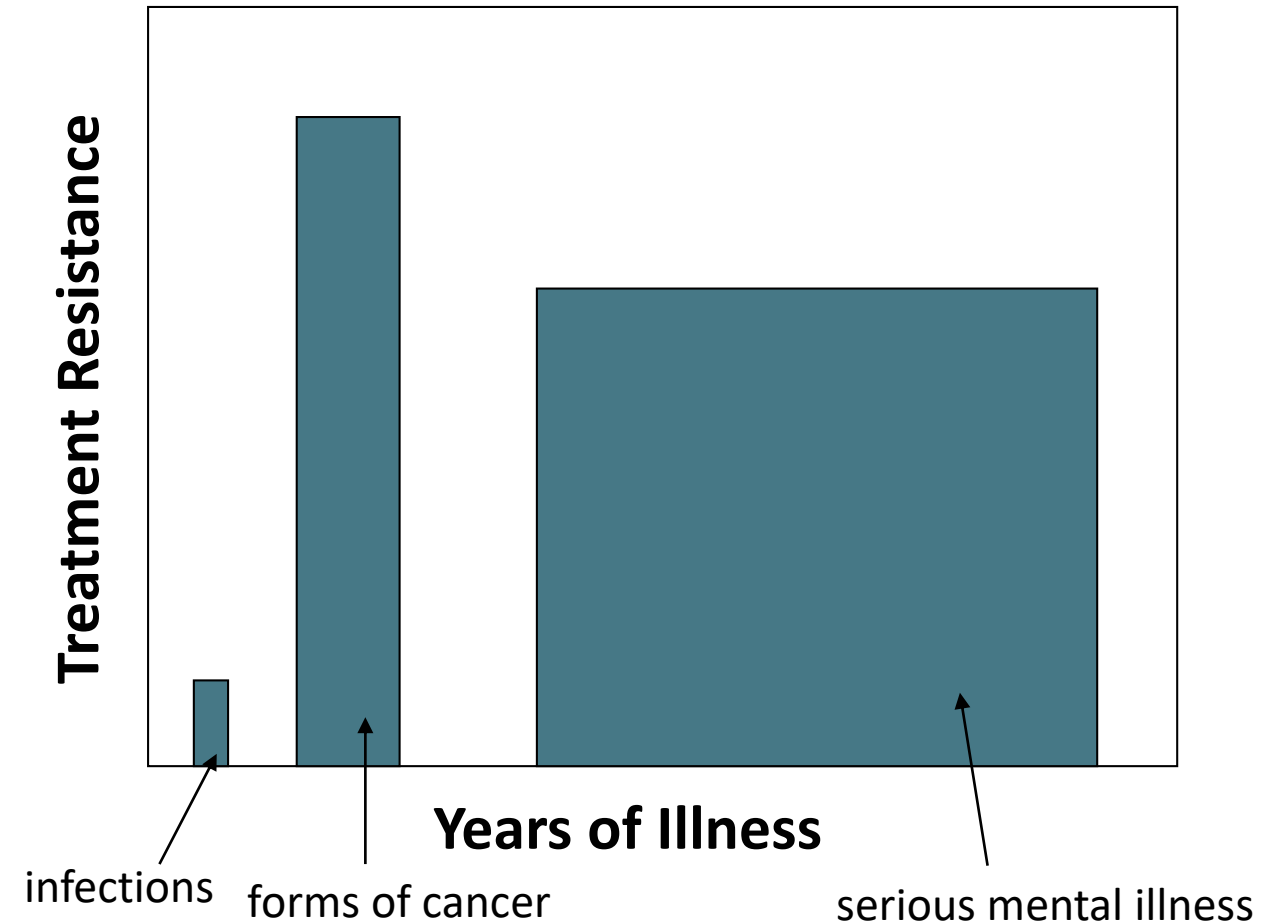
Rare implementation of prevention strategies in the real world

~ 2% of total spending on mental health is used for prevention

What is the case for prevention in mental health?

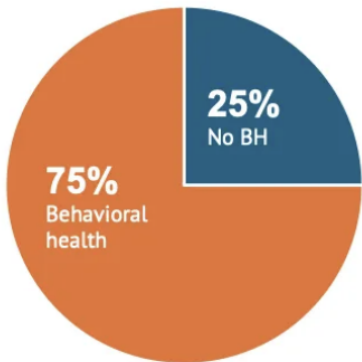
- Psychiatric illnesses are often chronic, disabling and highly costly to society
- These illnesses typically begin during the first three decades of life → can lead to many years of chronic illness
- Psychiatric illnesses are very common: > 25% of the population receives a psychiatric diagnosis during their lifetime
- Established risk factors, many of which are transdiagnostic, which can be associated with greater cost-effectiveness of prevention approaches
- Some evidence for efficacy of preventive interventions

Health Care Costs



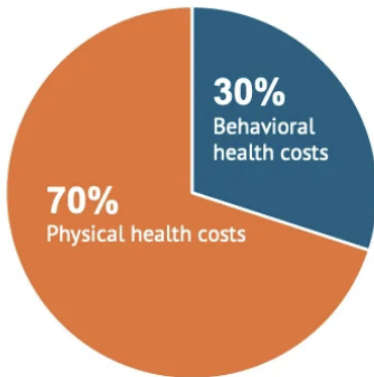
Overall healthcare costs are highest in those with chronic mental illnesses

75% of highest cost members have a chronic behavioral health condition



40% have SMI

70% of spending for members with BH conditions is related to physical health



Driven by ED and inpatient

Data courtesy of Vanna Health, based on public and commercial claims

Insel, “Healing: Our path from mental illness to mental health”

What are the **barriers** to implementing prevention programs for mental health?

- **Lack of established biomarkers** of illnesses that can be targeted
- **Stigma** –lack of acceptance of mental health screening programs
- **Little/no insurance reimbursement** of preventive mental health care
- **Unclear efficacy** of preventive interventions
- Treatments of psychiatric conditions are still under-resourced and under-utilized – why invest in prevention then?

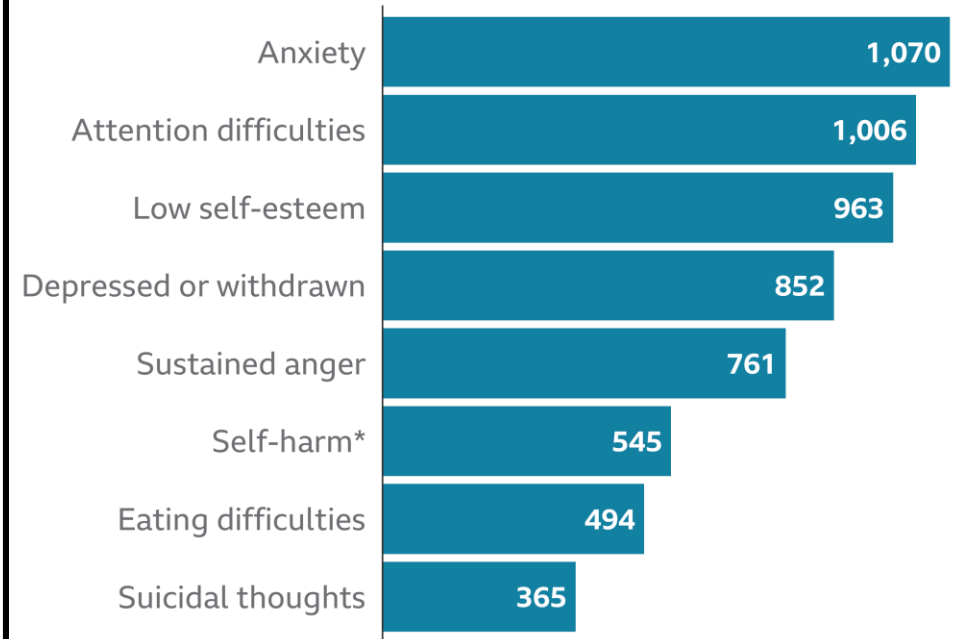


A youth mental health crisis

- A child and adolescent mental health **national emergency** declared in late 2021
- Declared by the American academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry, and the Children's Hospital Association
- Enormous increase in pediatric mental health ER visits, doubling rates in the previous 10 years
- Also a 5-fold increase in ER visits specifically related to suicide in young people

Almost all staff surveyed saw increases in mental health problems among pupils

Number of staff who said they had seen a substantial or slight increase since the start of the autumn term



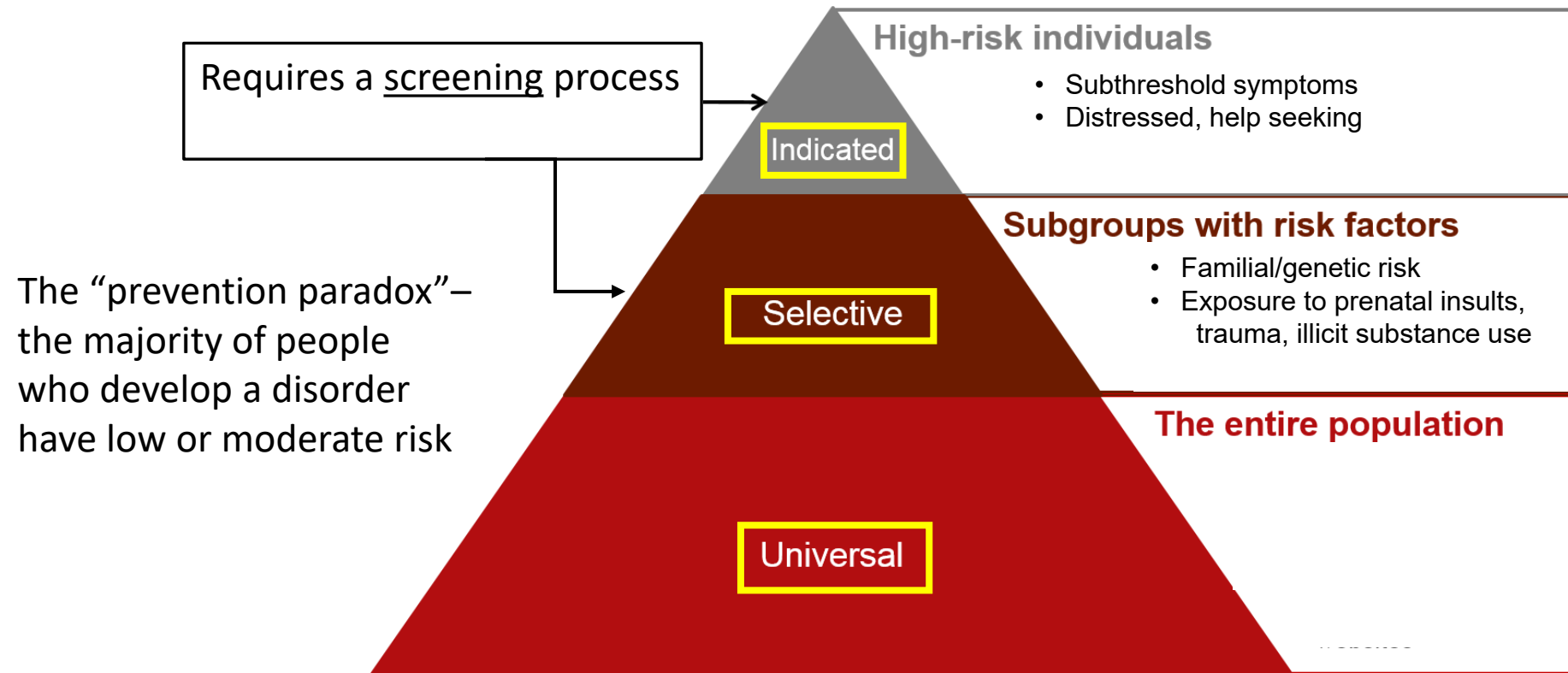
*Self-harm/self-destructive thoughts or acts
Survey of 1,130 teaching and support staff conducted in January 2022

Source: NAHT, Place2Be

BBC

Prevention in Psychiatry: how could it work?

3 categories of *primary* prevention strategies in medicine:



Also:
-secondary prevention
-tertiary prevention

Gordon, Pub Health Rep 1983

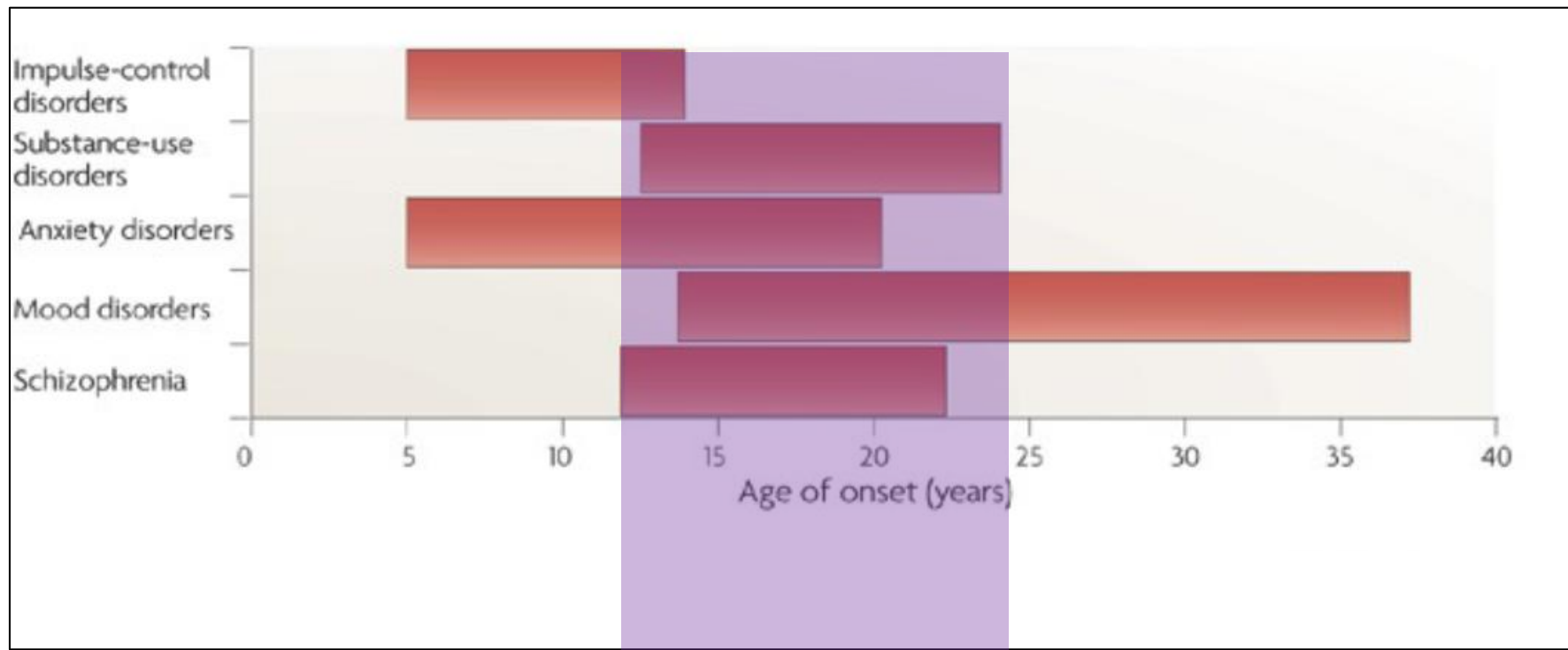
Examples of the three types of prevention

Type of Prevention	Risk Factors	Examples in General Medicine	Examples within Psychiatry
Universal	None	Cancer and cardiovascular disease screening in primary care; exercise and healthy eating public education and school-based programs	Depression and maltreatment screening in primary care settings; social and emotional learning school-based programs
Selective	‘Silent’	More frequent monitoring of those with a family history of mid-life cancer, cardiovascular disease, or genetic markers of those conditions; interventions for individuals with familial/genetic risk for dementia	Early intervention (e.g., home visits) for infants or toddlers with risk factors for developmental issues or maltreatment; support and psychoeducation for family members of people with serious mental illnesses
Indicated	Early signs of symptoms of illness	Removal of precancerous lesions; lifestyle, pharmacological interventions for those with early symptoms/signs of cardiovascular disease	Intervention programs for individuals with subclinical symptoms of psychosis (those at “clinical high risk” for developing a psychotic disorder)

Holt & DeTore, Psych Annals 2021

When to intervene?

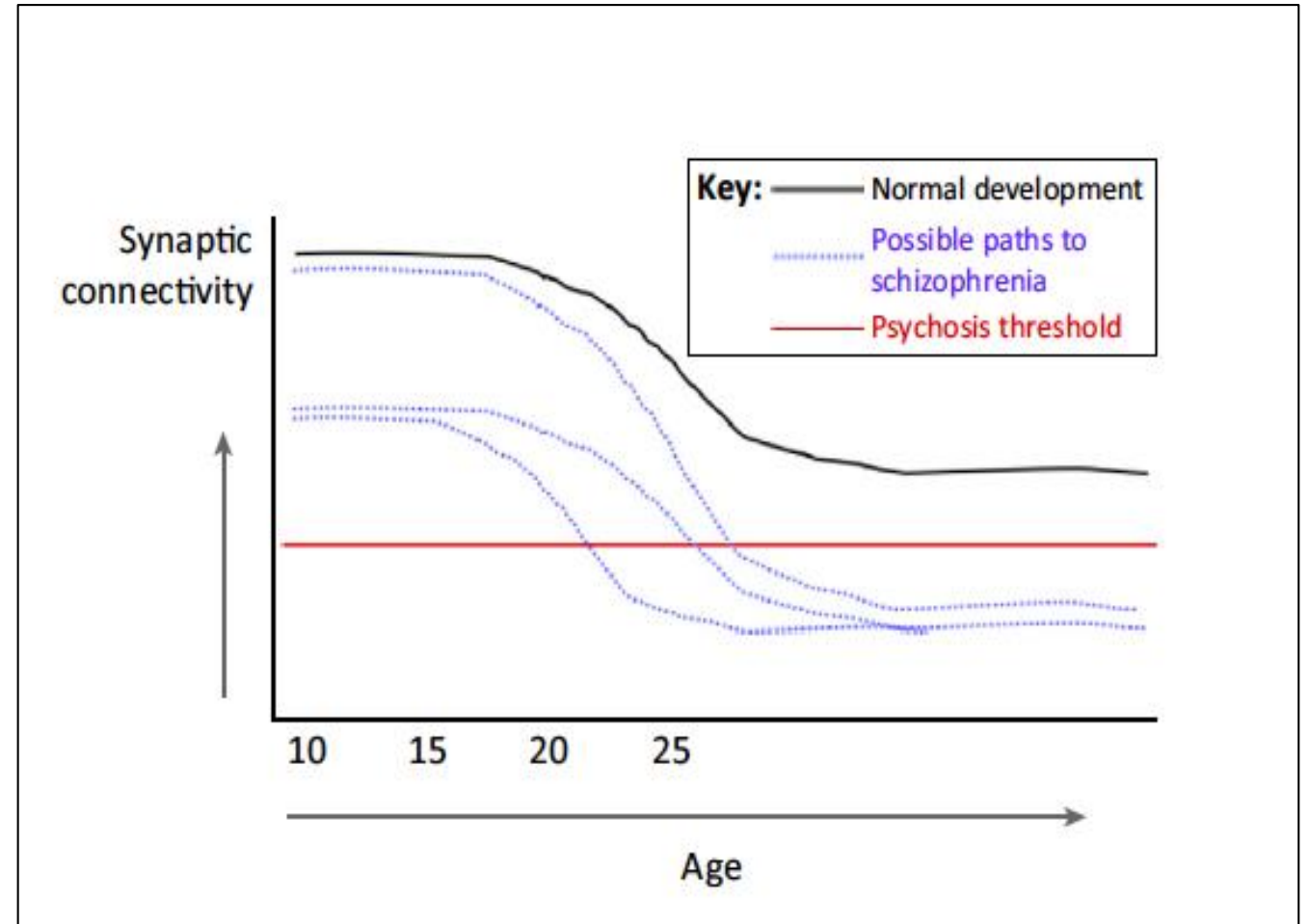
Adolescence and early adulthood is a time of life when many mental illnesses emerge for the first time - perhaps the best time window for prevention efforts?



Paus, Keshevan and Geid, Nat Rev Neurosci 2008

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

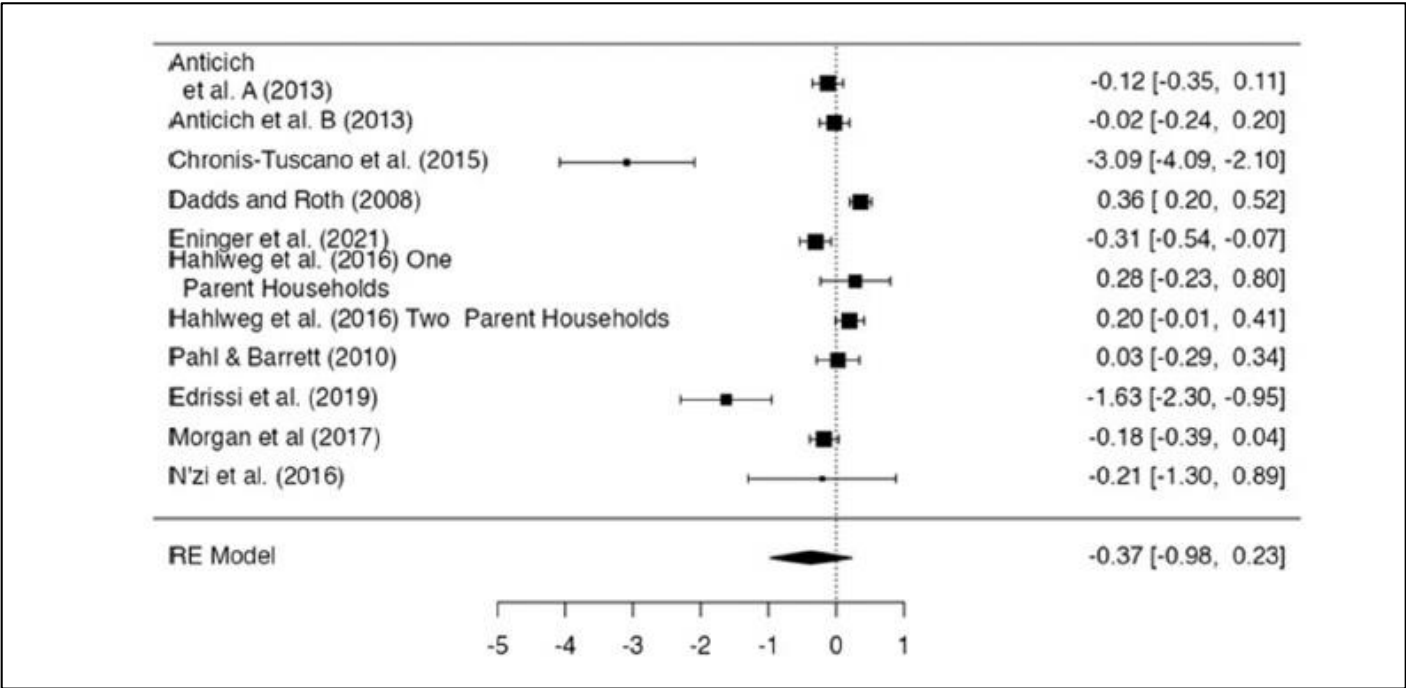
- may be due to a greater sensitivity of the brain to the effects of hormonal changes and stress
- or an acceleration of the loss of synapses that normally occurs during this period



Cannon, TICS 2015

Prevention in early childhood

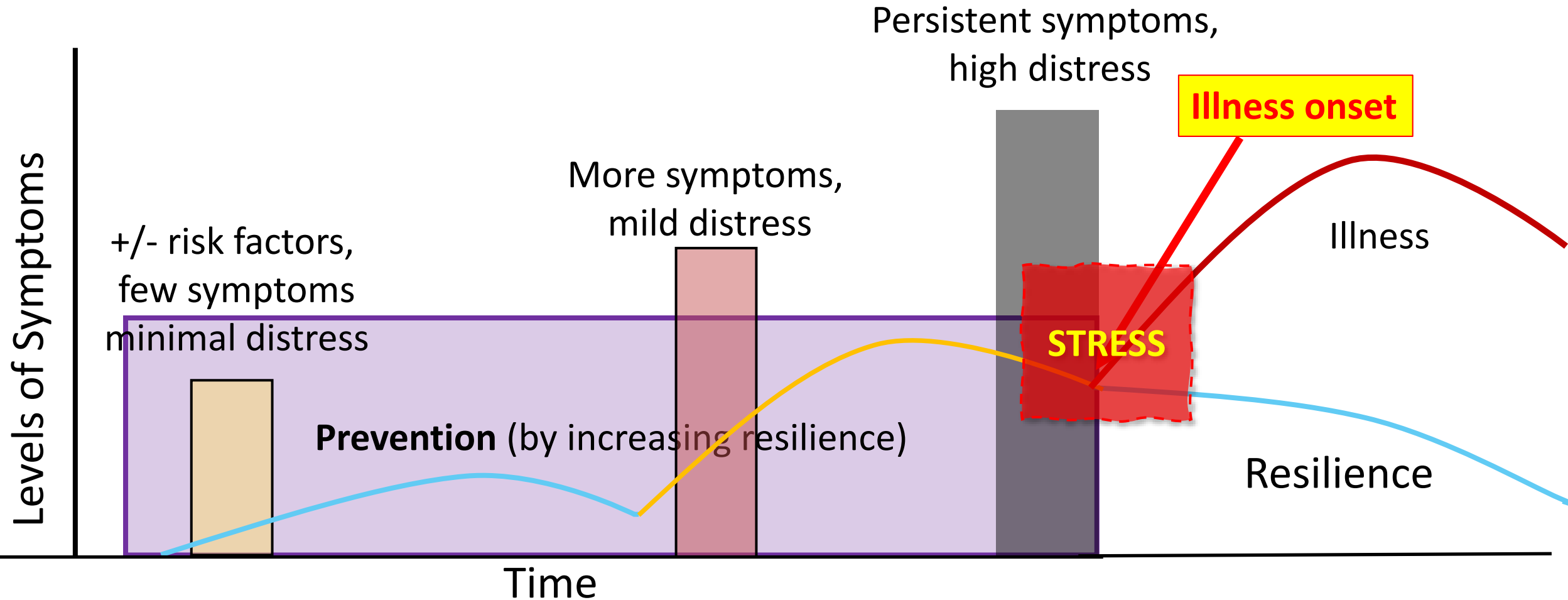
Meta-analysis of studies of the prevention of internalizing disorders in children 3-5 years old (17 trials):



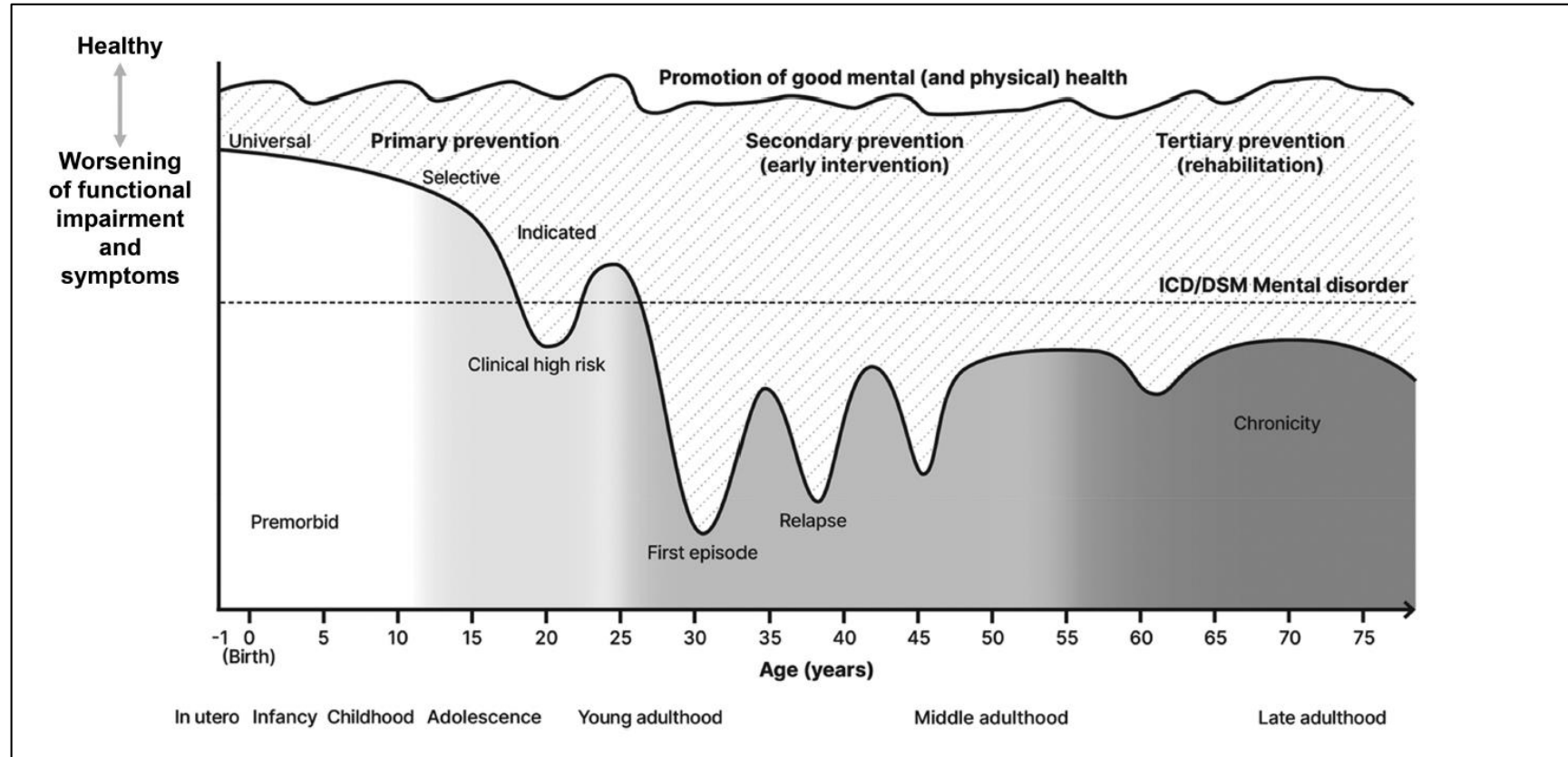
Small-to-moderate effect size at 6-7 months post intervention, but not at 12 months

Bolton et al, Front Psych, 2023

When to intervene?



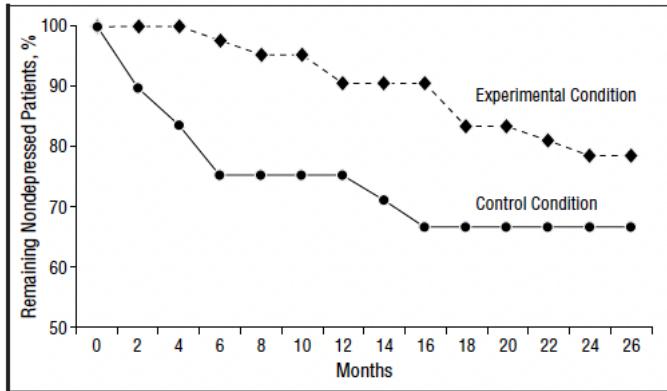
Different prevention strategies could target different phases of pre-illness/illness



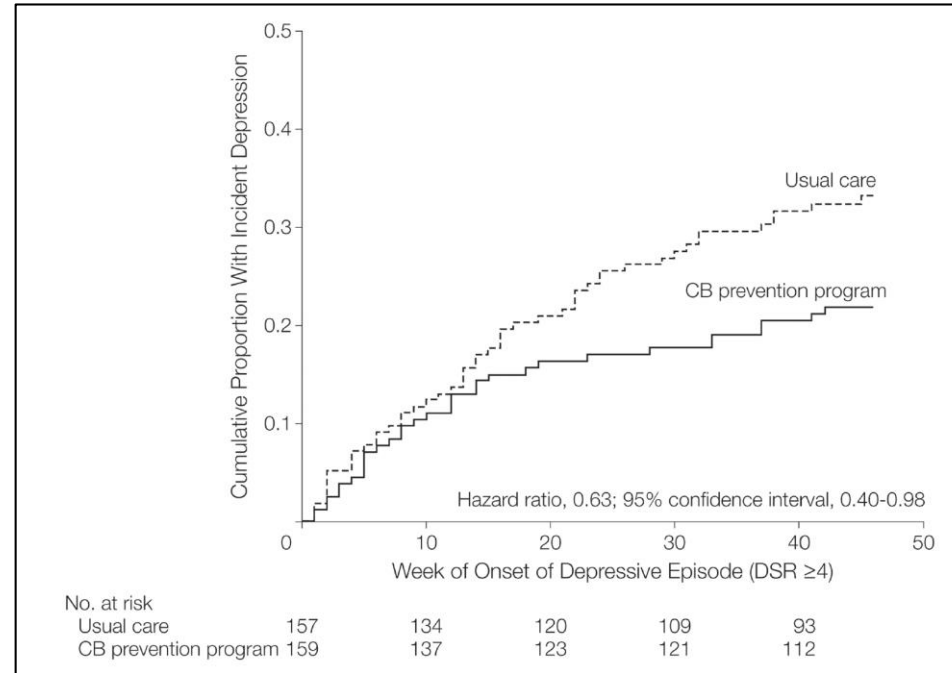
Fusar Poli et al, World Psych 2021

But what is the evidence that psychiatric disorders can be prevented?

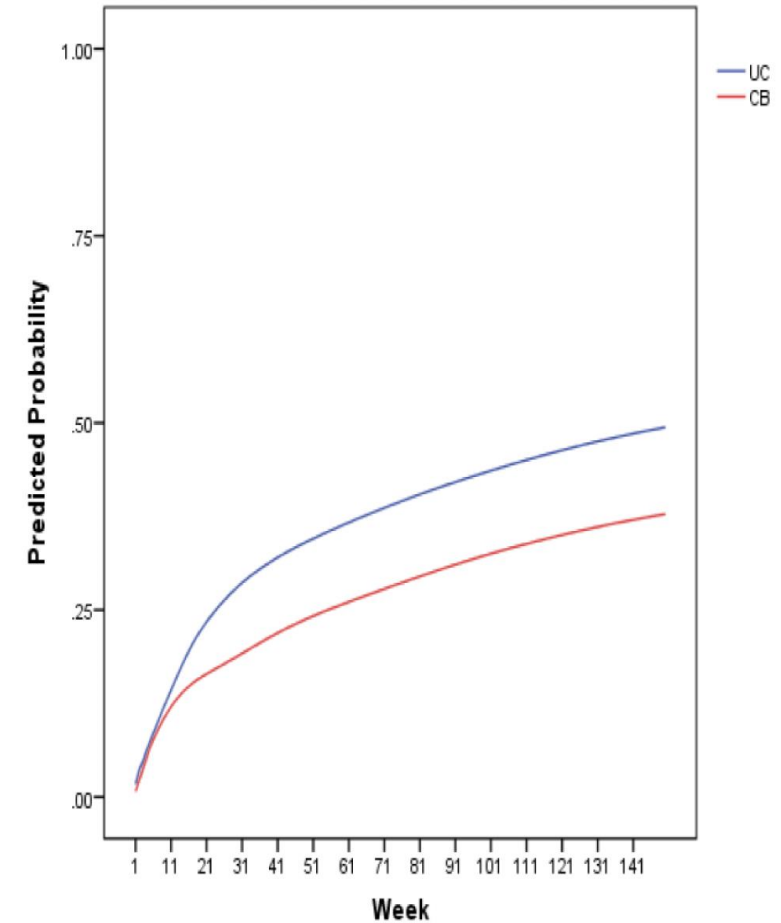
Consistent evidence that **depression** can be prevented



Clarke et al, Arch Gen Psych, 2001



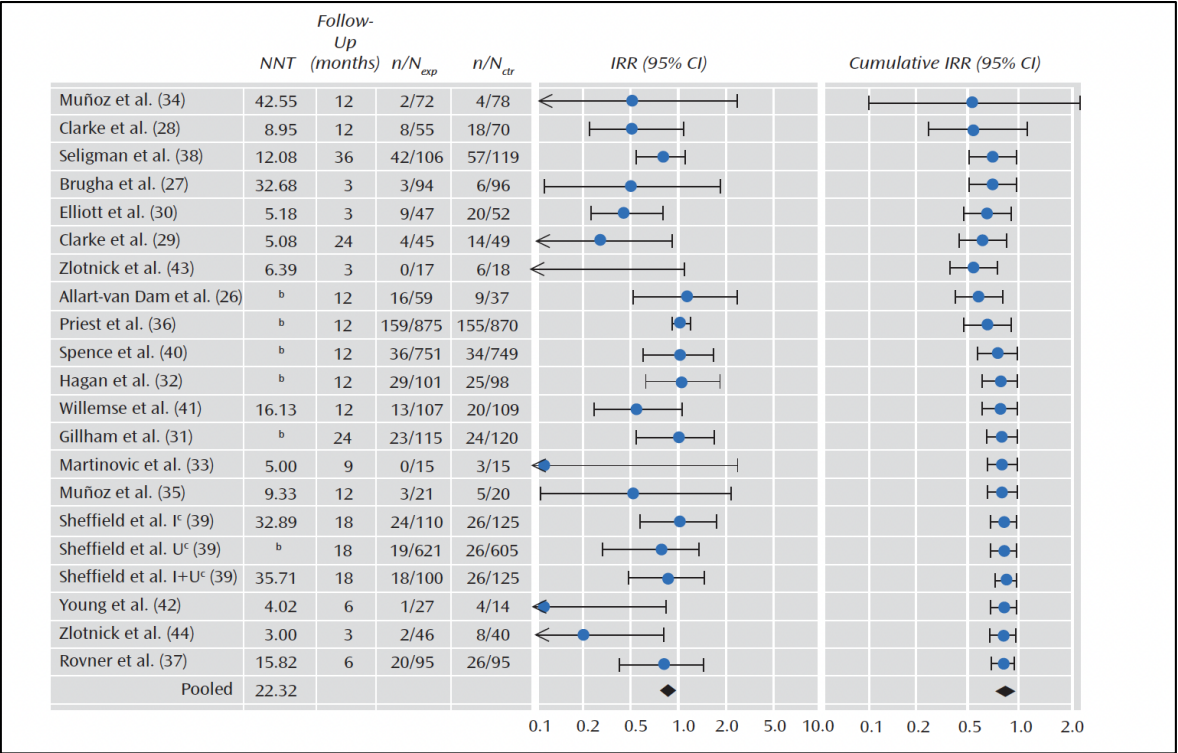
Garber et al, JAMA 2009



Beardslee et al, JAMA Psych 2013

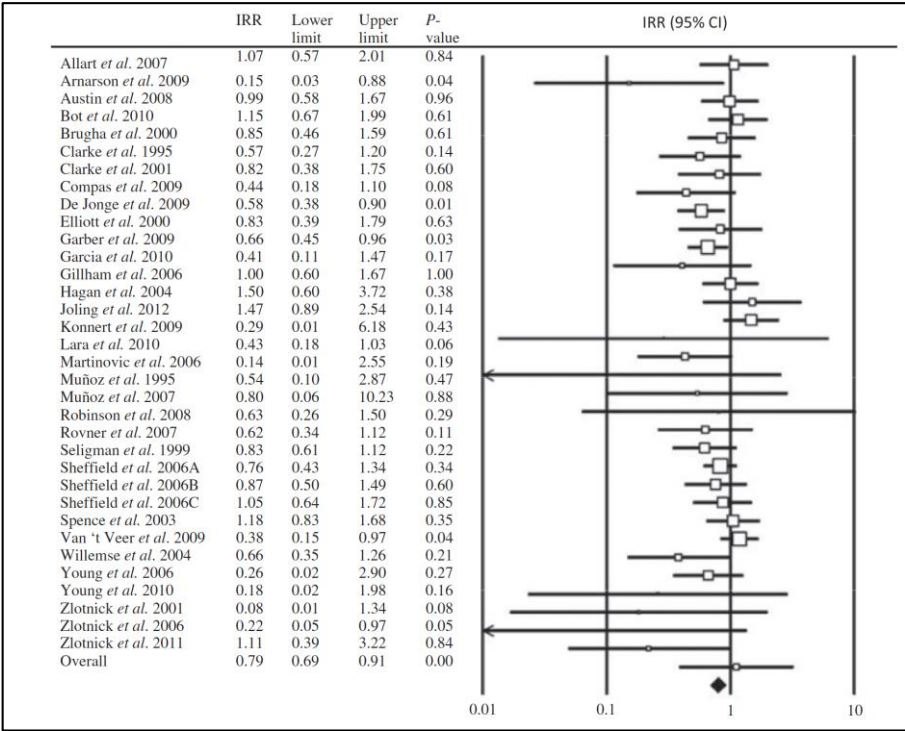
Meta-analyses consistently show small to moderate effect sizes for depression prevention (with behavioral interventions)

Meta-analysis of 19 studies –
reduction of the incidence of depression by 22%



Cuijpers et al, Am J Psych 2008

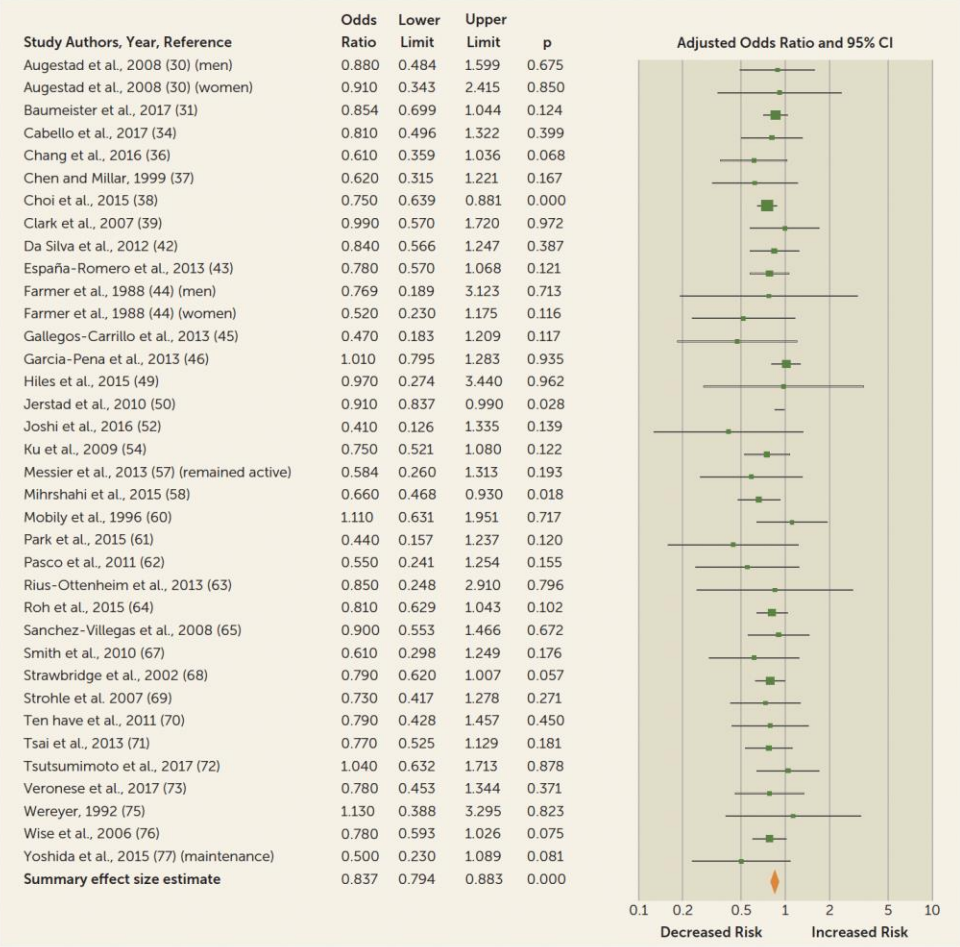
Updated meta-analysis of 32 studies –
reduction in incidence of depression by 21%



Van Zoonen et al, Int J Epidem 2014

Physical activity protects against depression

Meta-analysis of 49 studies, N= ~277K,
average follow-up 7.4 years



Schuch et al, Am J Psych 2018

Review of 8 meta-analyses,
134 studies of exercise-related interventions in at-risk groups

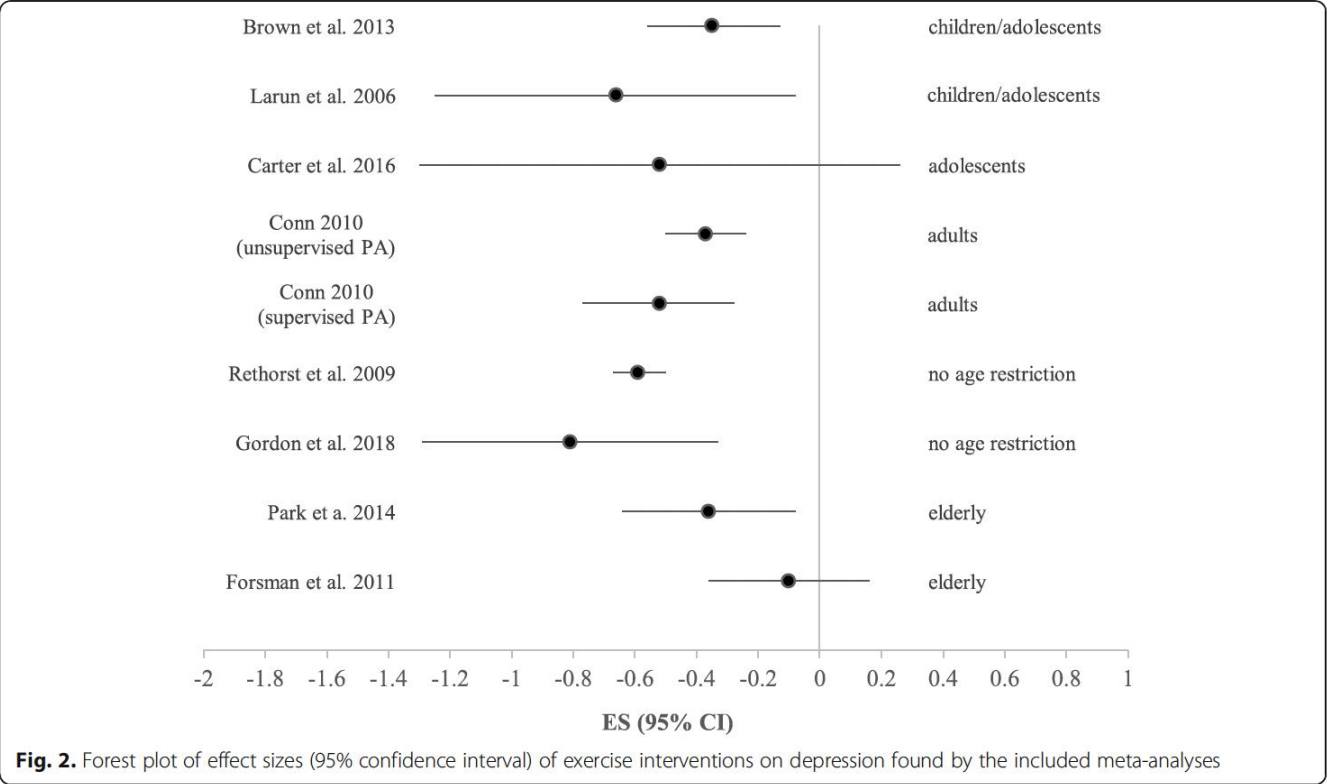


Fig. 2. Forest plot of effect sizes (95% confidence interval) of exercise interventions on depression found by the included meta-analyses

Hu et al, BMC Pub Health, 2020

Limitations of depression prevention efforts to date

- Modest size of effects
- Limited follow-up periods, length of effects unclear (delay vs. prevention)
- Unclear efficacy of universal prevention programs, selective and indicated have stronger effects but lower uptake
- Low uptake/engagement/satisfaction for some interventions – not “youth friendly” enough? Effects of stigma?

Cuijpers, Curr Dir Psych Sci, 2024



“Indirect” approaches may increase engagement

- Focus on topics indirectly related to mental health that may be important to youth

- Bullying
- Stress management
- Perfectionism
- Relationships
- Procrastination
- Test taking
- Sleep

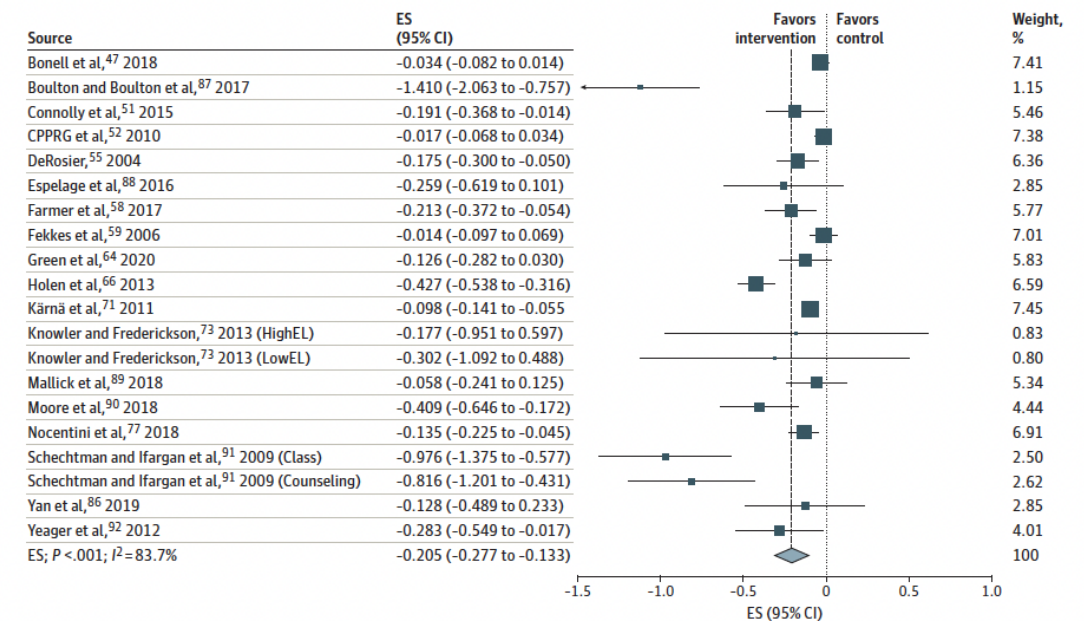
- Co-design interventions with youth collaborators

Cuijpers, Clin Psych Eur, 2021;

Birrell et al, Child Adol Mental Health, 2025

For example, anti-bullying programs
reduce bullying and *improve mental health*

Figure 2. Effectiveness of Anti-Bullying Interventions on Mental Health Problems at Study End Point



Fraguas et al, JAMA Pediatrics, 2021

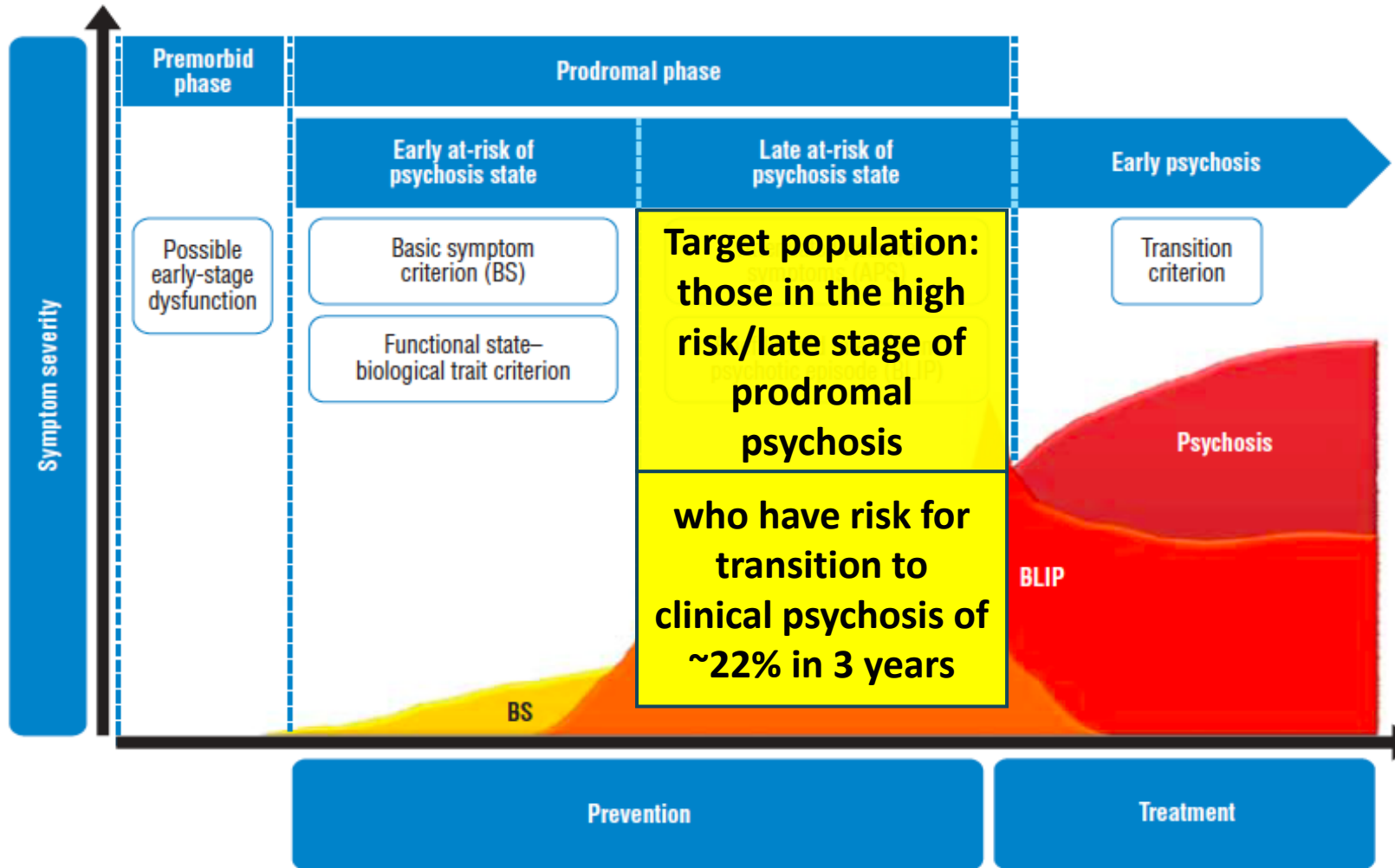
What about preventing psychosis?

- Interventions most often tested to date for their efficacy in preventing the onset of psychosis:
 - Antipsychotic medication
 - Cognitive behavioral therapy (CBT) and related psychosocial interventions
 - Nutritional supplements, e.g., omega-3-fatty acids (fish oil)
- Target at-risk group: individuals with subsyndromal psychotic symptoms, who are in distress, help-seeking
 - “Ultra-High Risk” (UHR) or “Clinical High Risk” (CHR)
 - *Indicated* prevention (targeting a high-risk group)



fish oil supplements

What about preventing psychosis?

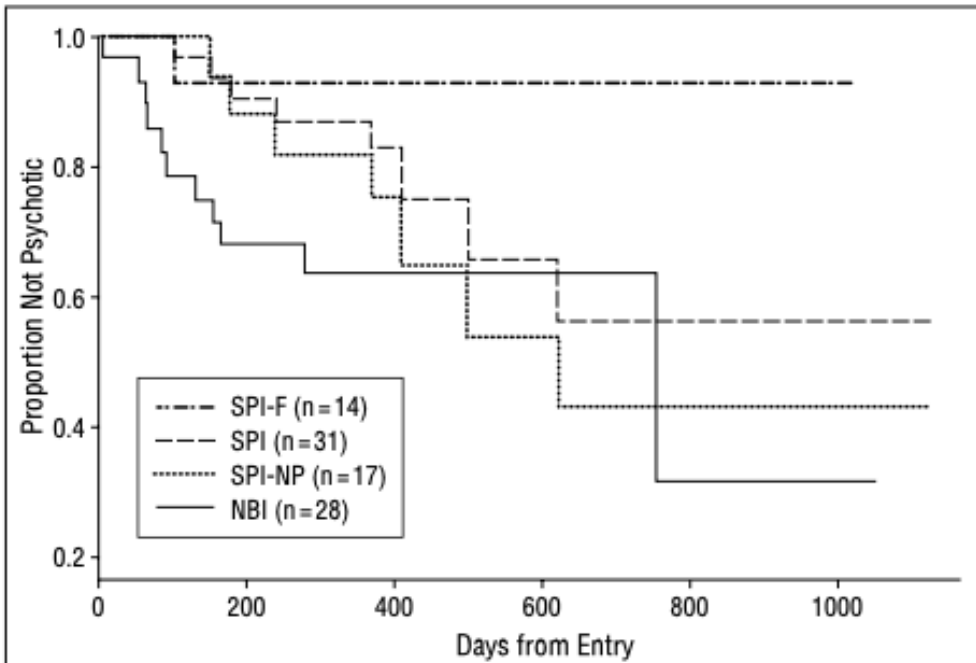


Fusar-Poli, JAMA Psych 2013

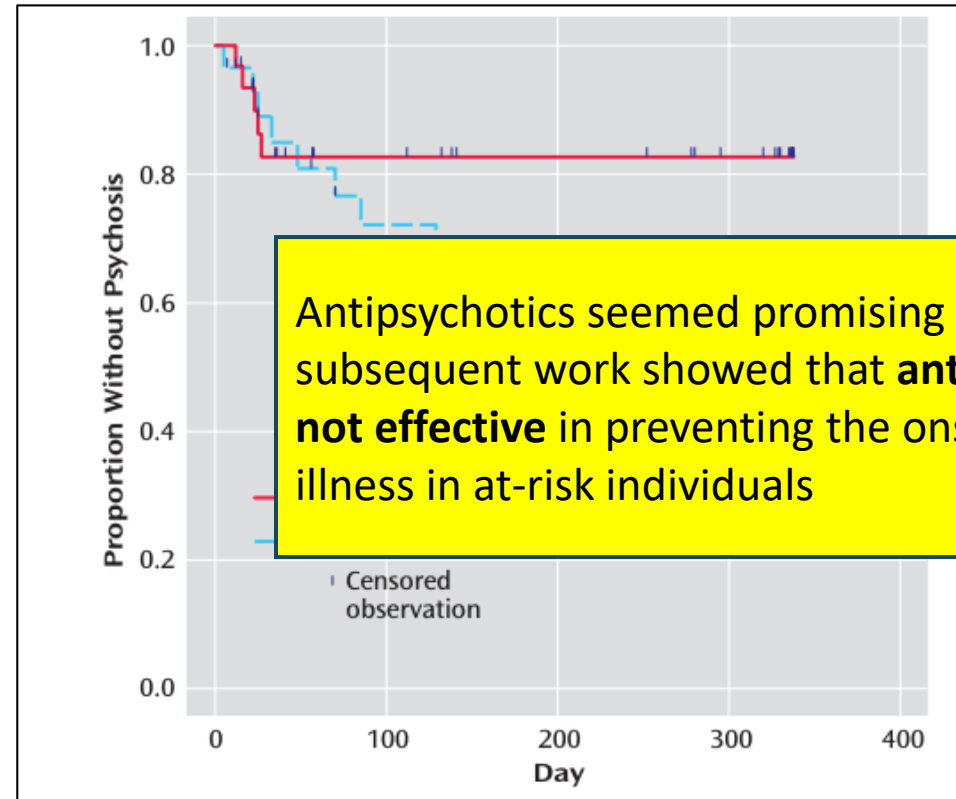
Fusar-Poli, et al 2020, review of 42 meta-analyses of CHR/UHR population:

- Mean age: 20.6 years
- 58% male
- Transition to psychosis predicted by severity of attenuated psychotic and negative symptoms, low functioning
- comorbidity high: 41% depression, 66% suicidality, 27% cannabis users
- 87% with history of trauma

Can antipsychotic medication prevent psychosis? No



McGorry et al, Arch Gen Psych 2002



McGlashan et al, Am J Psych 2006

Can Cognitive Behavioral Therapy (CBT) prevent psychosis? Maybe... results have been variable

One small positive trial

Treatment group	PANSS transition <i>n</i> (%)	Antipsychotic medication <i>n</i> (%)	DSM–IV psychosis diagnosis <i>n</i> (%)
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, <i>N</i> (%)	PANSS Transition, <i>N</i> (%)	Antipsychotic Medication, <i>N</i> (%)	<i>DSM-IV</i> Psychotic Diagnosis, <i>N</i> (%)
Cognitive therapy (<i>N</i> = 35)	17 (49)	7 (20)	5 (14)	7 (20)
Monitoring (<i>N</i> = 23)	10 (43)	5 (22)	8 (35)	7 (30)

Morrison et al, Schiz Bull 2007

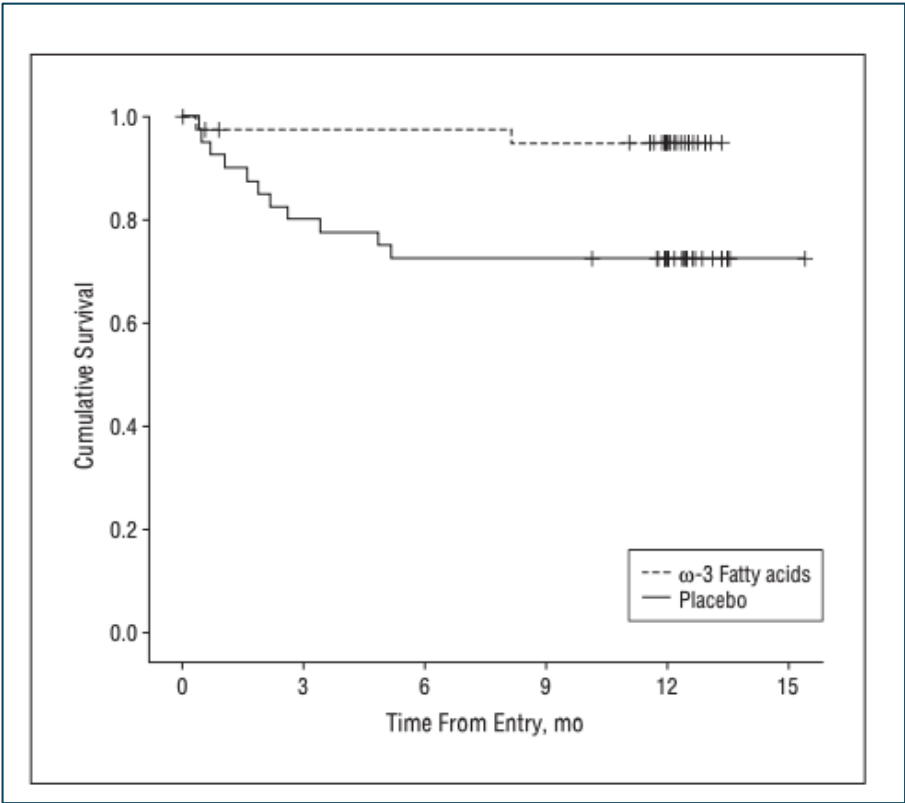
Then a larger, multi-site trial was negative...

Group	Month of assessment											
	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

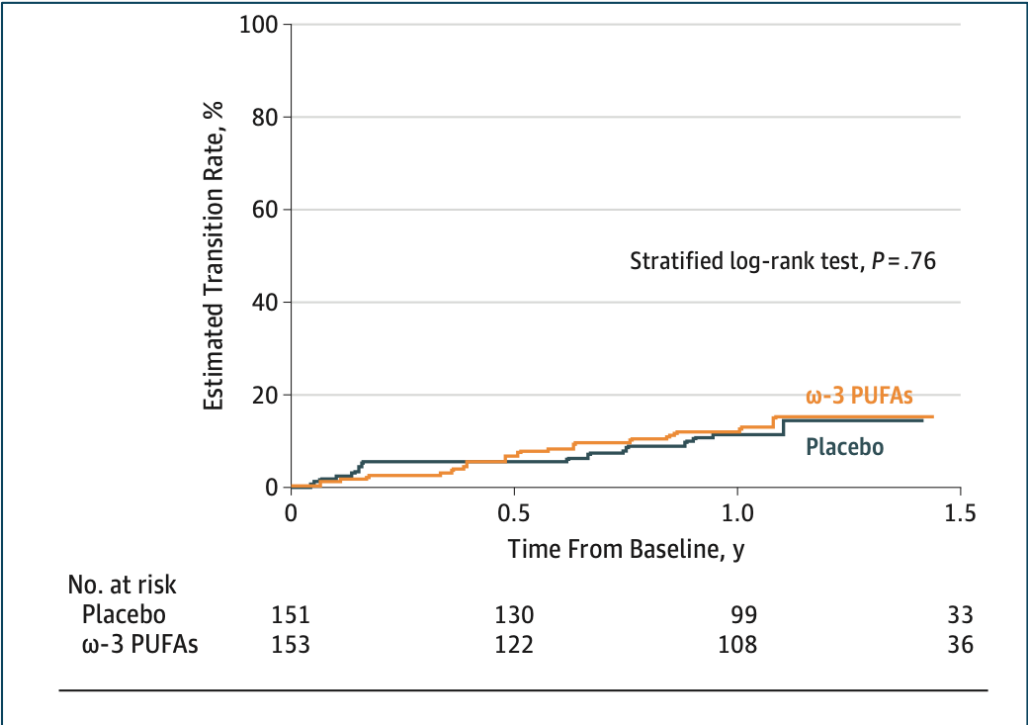
Can Omega-3-Fatty Acids prevent psychosis?

One positive trial was not replicated



Amminger et al, Arch Gen Psych 2010

the NEURAPRO trial



McGorry et al, JAMA Psych 2017

In the NEURAPRO trial, greater increases in omega-3-fatty acids predicted greater clinical improvement (Amminger et al, Biol Psych 2019)

Inconsistent findings of different meta-analyses: who is correct?

Lack of evidence

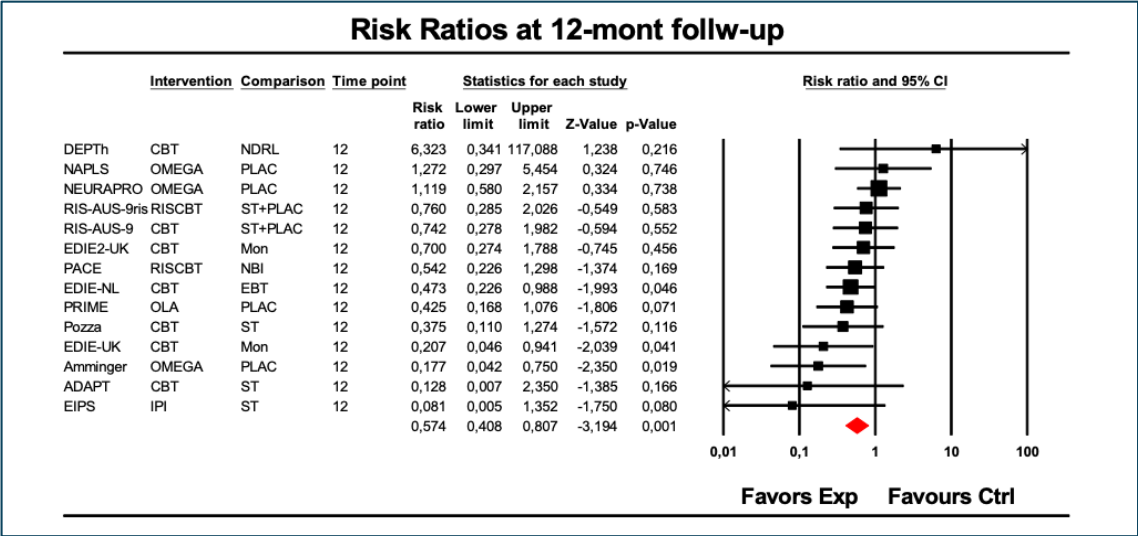
to favor specific preventive interventions
in psychosis: a network meta-analysis

Cathy Davies¹, Andrea Cipriani², John P.A. Ioannidis³⁻⁷, Joaquim Radua^{1,8,9}, Daniel Stahl¹⁰, Umberto Provenzano^{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

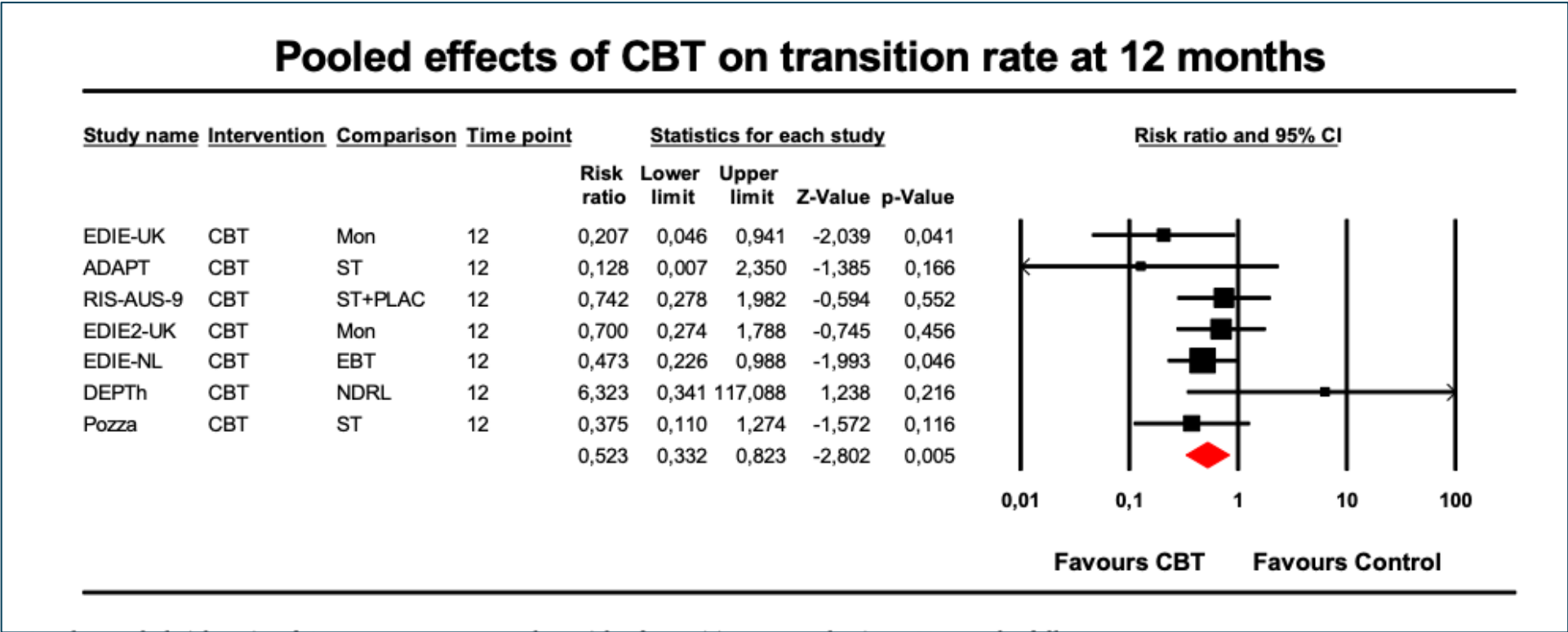
However, a pooling of studies using different interventions produced a different result... reduction of the risk for transition to psychosis of 43%

No significant effects on functioning, quality of life



Mei et al, Clin Psych Rev, 2021

Specifically, **CBT** may have a preventive or delaying effect on transition to psychosis

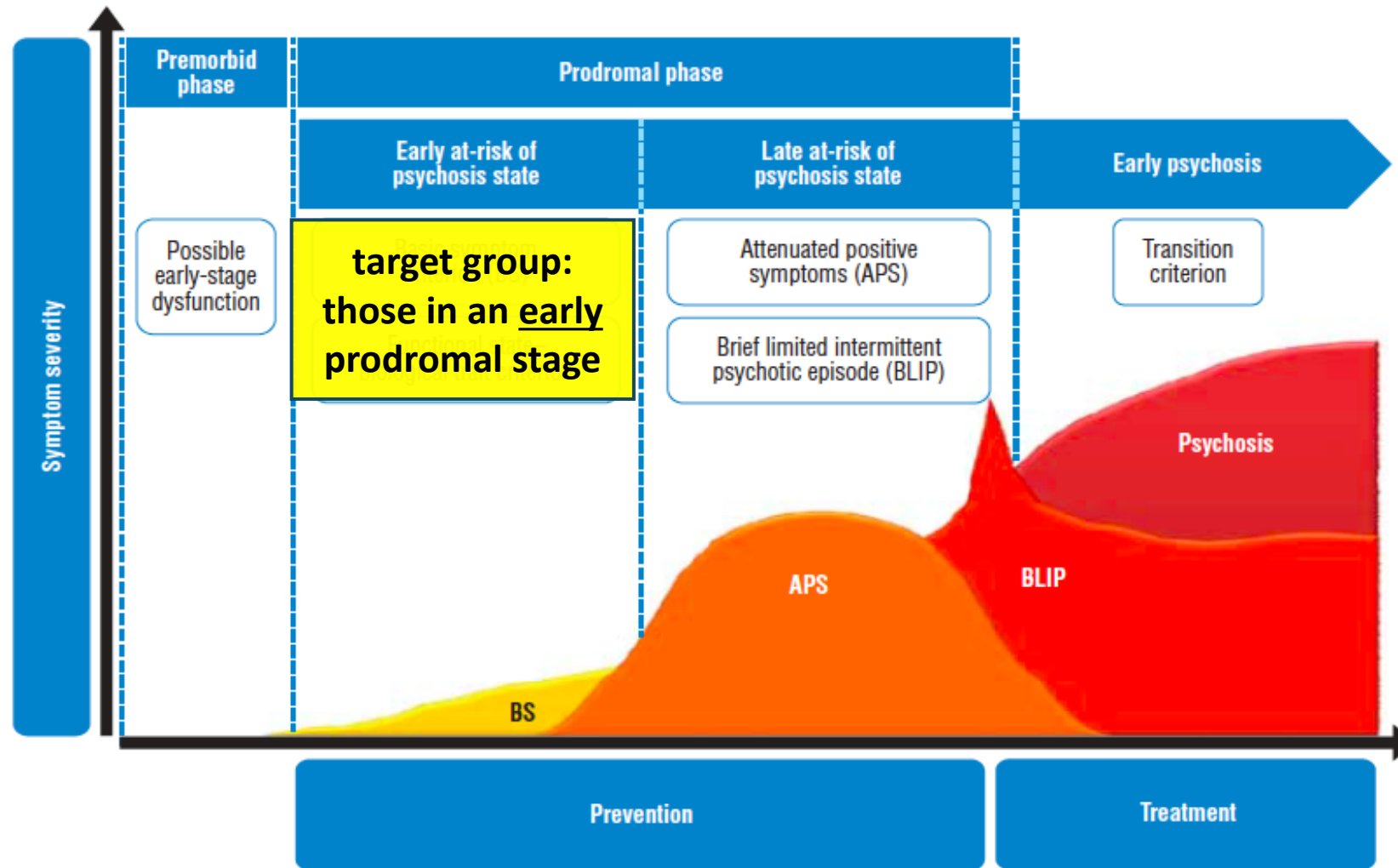


Mei et al, Clin Psych Rev, 2021

What are the reasons for the 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

What about intervening earlier?



Fusar-Poli, JAMA Psych 2013

New prevention strategy: Targeting “transdiagnostic” at-risk states

“pluripotential at-risk mental state”

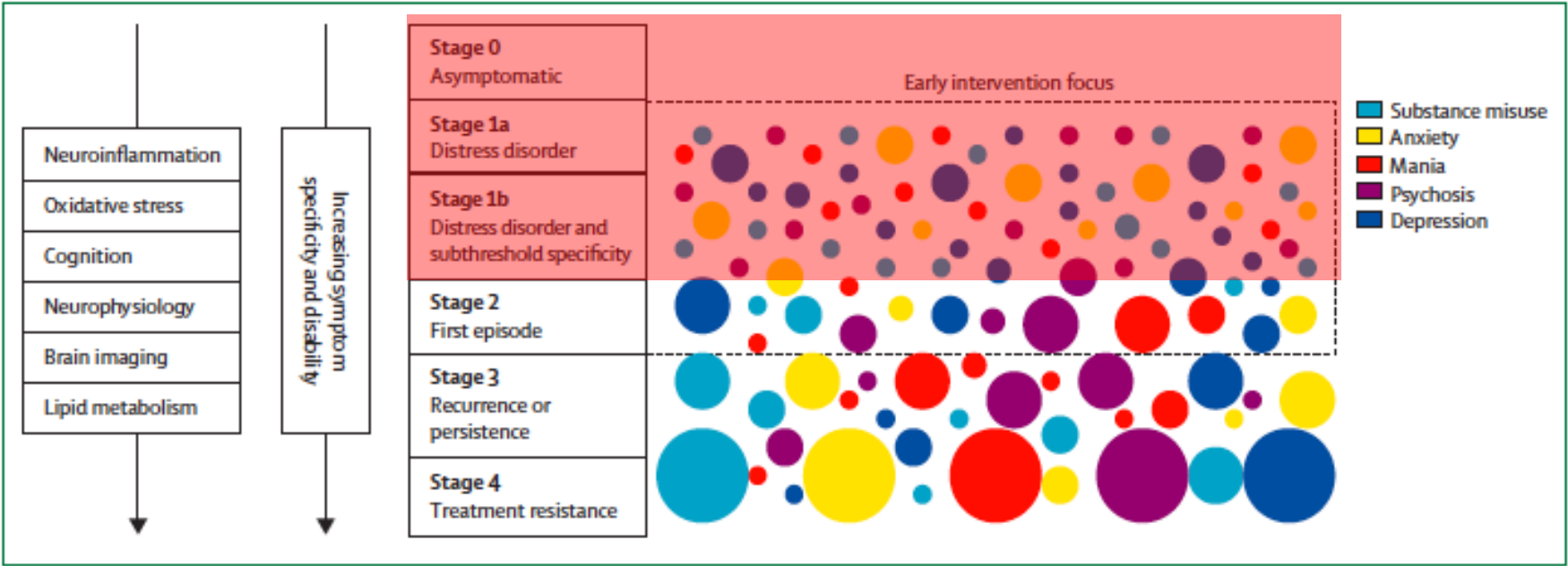
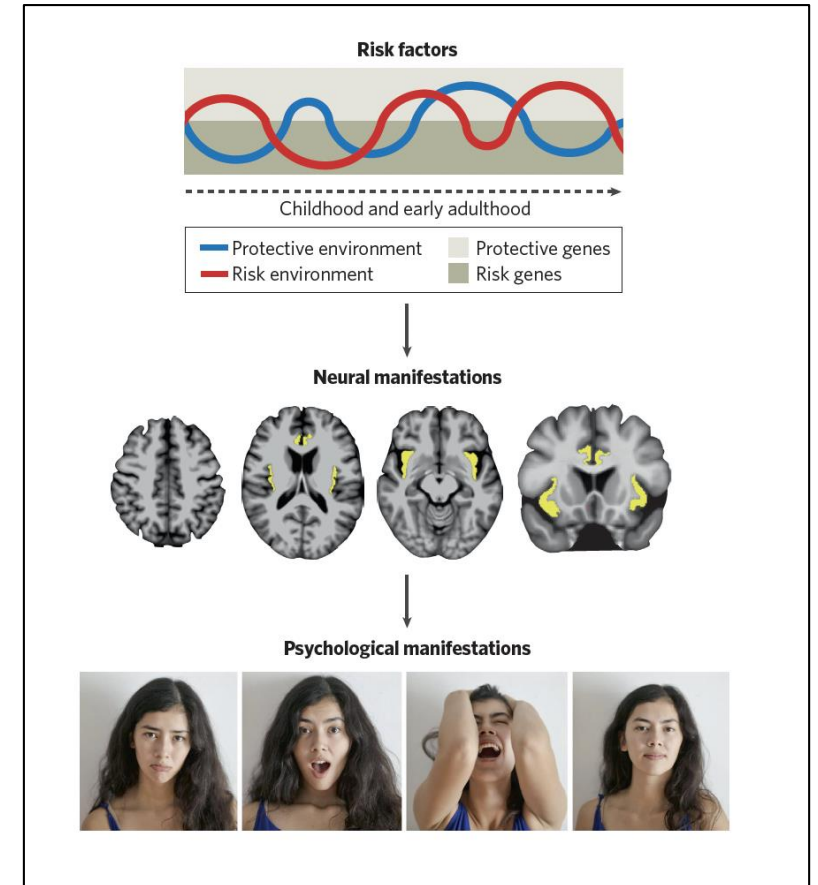


Figure: Biomarkers and clinical staging in psychiatry

Nieman & McGorry, Lancet 2015

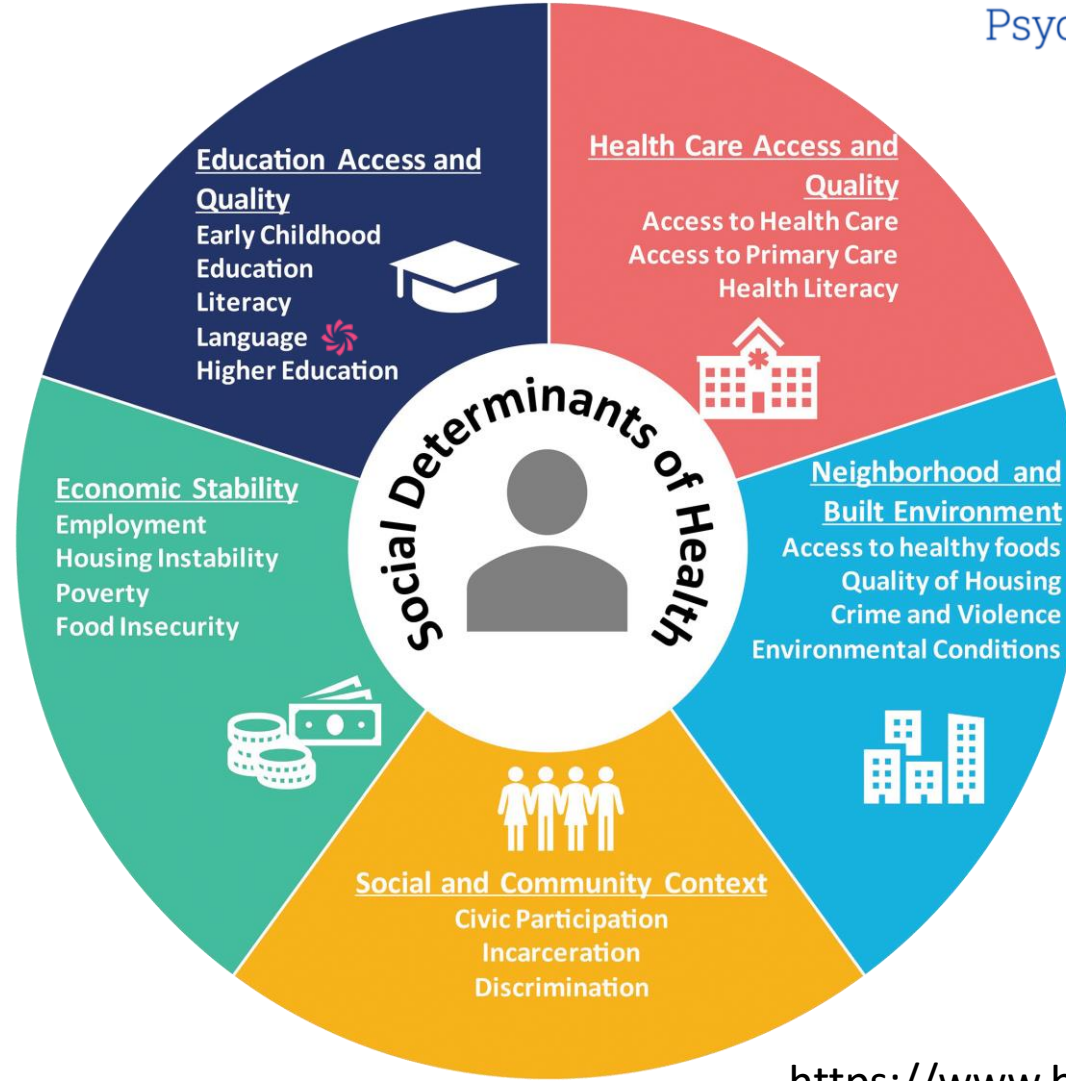
Transdiagnostic risk factors for mental illness

- **Genetic risk**
 - Common genetic variants associated with increased risk for numerous psychiatric disorders
- **Environmental risk**
 - Prenatal toxins/infections
 - Childhood neglect and abuse
 - Environmental exposures (e.g., nutritional, pollution, elicit substances)
- **Neural manifestations**
 - Changes in brain "hubs" with high degrees of connectivity
 - Vulnerability may be related to length of developmental course
- **Psychological manifestations**
 - High levels of comorbidity across psychiatric diagnoses—having more than one diagnosis is more common than not
 - Behavioral inhibition, negative affect, internalizing symptoms may precede other symptoms



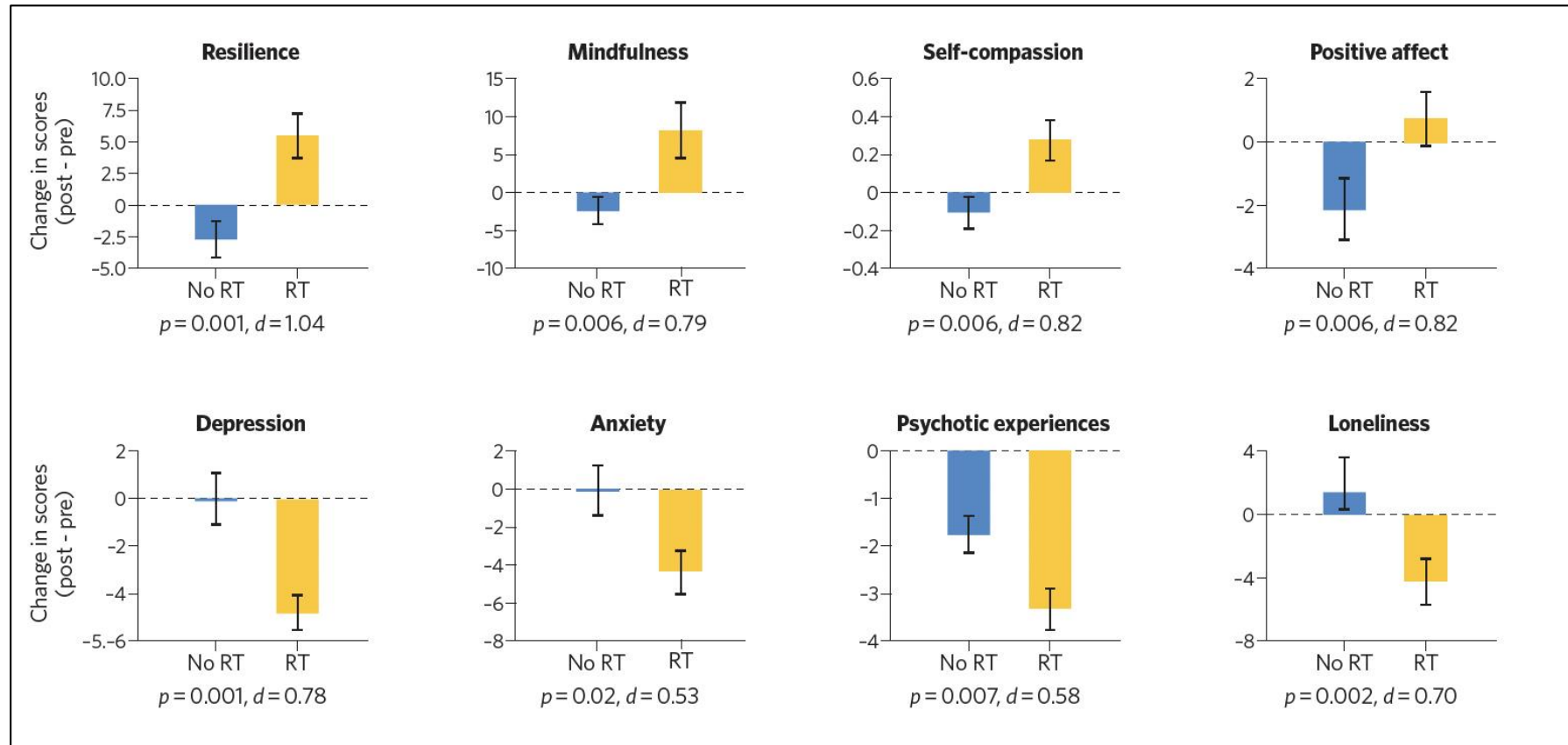
Holt et al, Neuropsychopharm Rev 2025

Social determinants of mental health



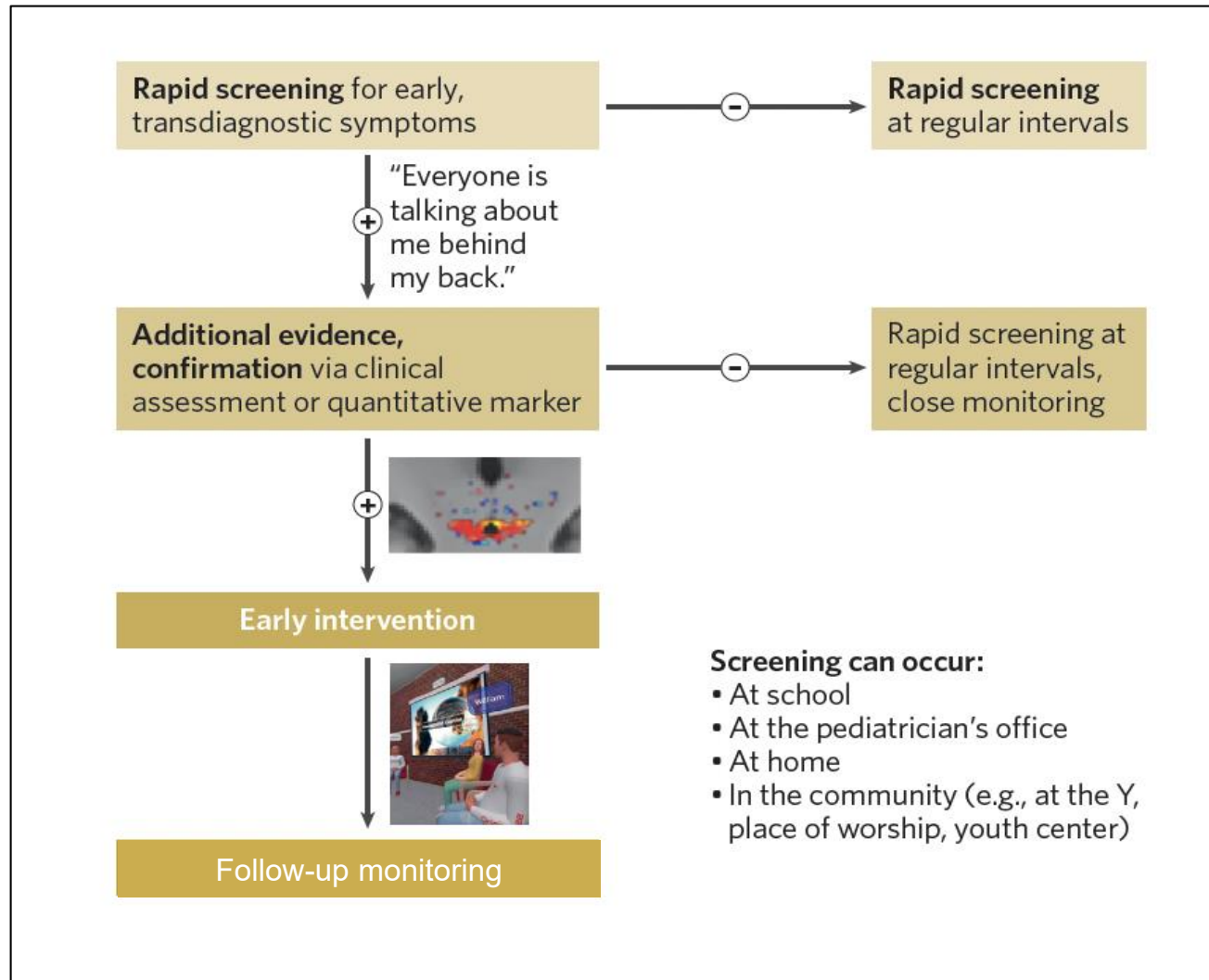
<https://www.bitterroothealth.org>

Behavioral interventions, e.g., Resilience Training, tailored for transdiagnostically at-risk youth can be protective



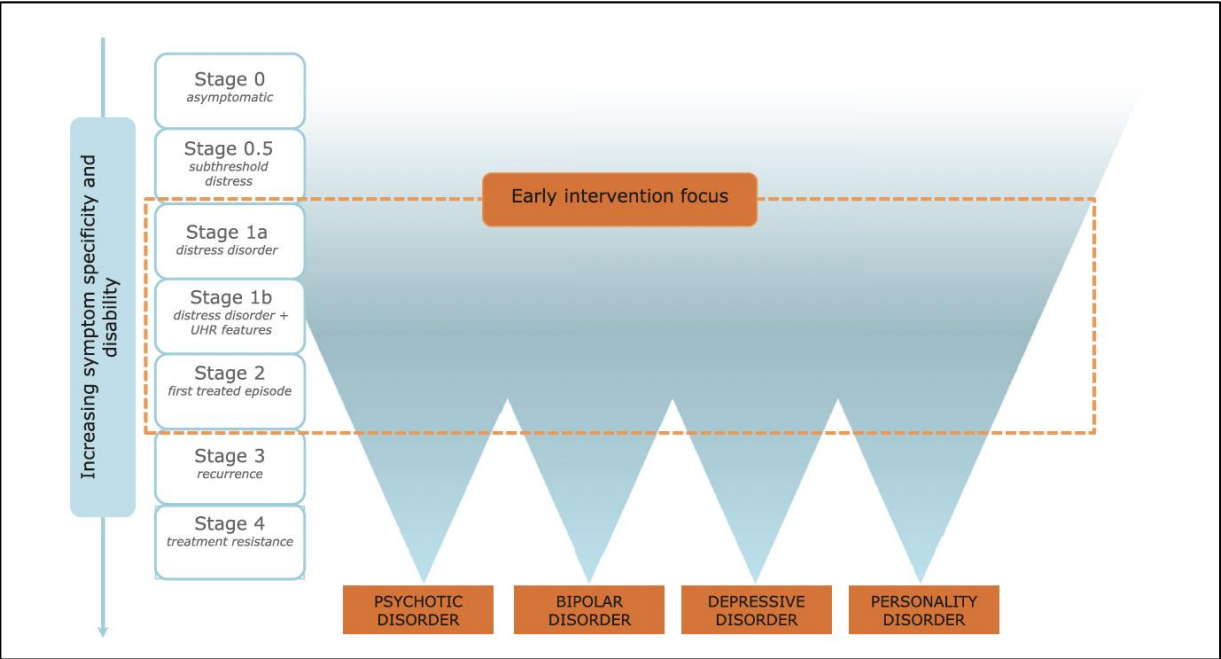
DeTore et al, 2022, 2024; Holt et al, 2024, 2025

A transdiagnostic model of screening, early detection and prevention

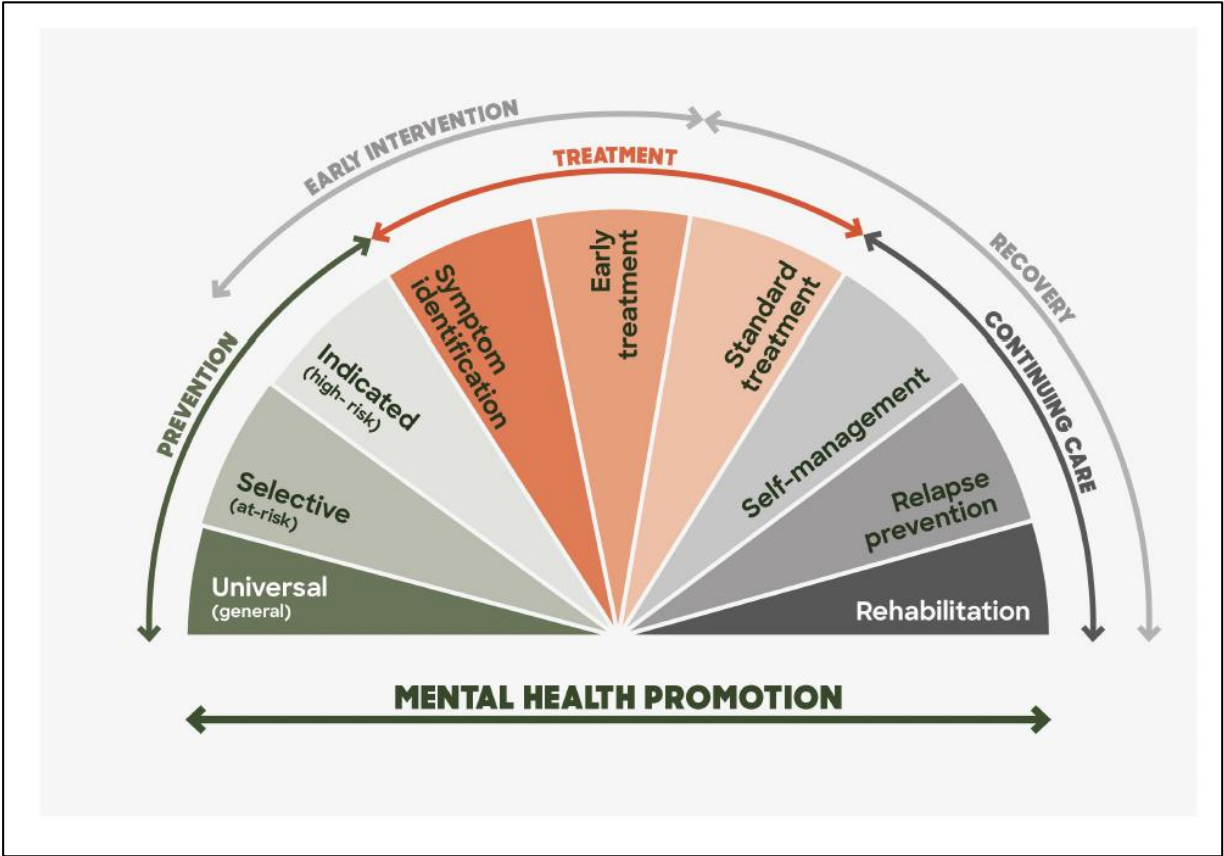


Holt et al, Neuropsychopharm Rev 2025

Integration with an overall program of *stage-based* mental health care



Hartmann et al, Ear Intervention Psych 2017



McGorry et al, Front Psych 2024

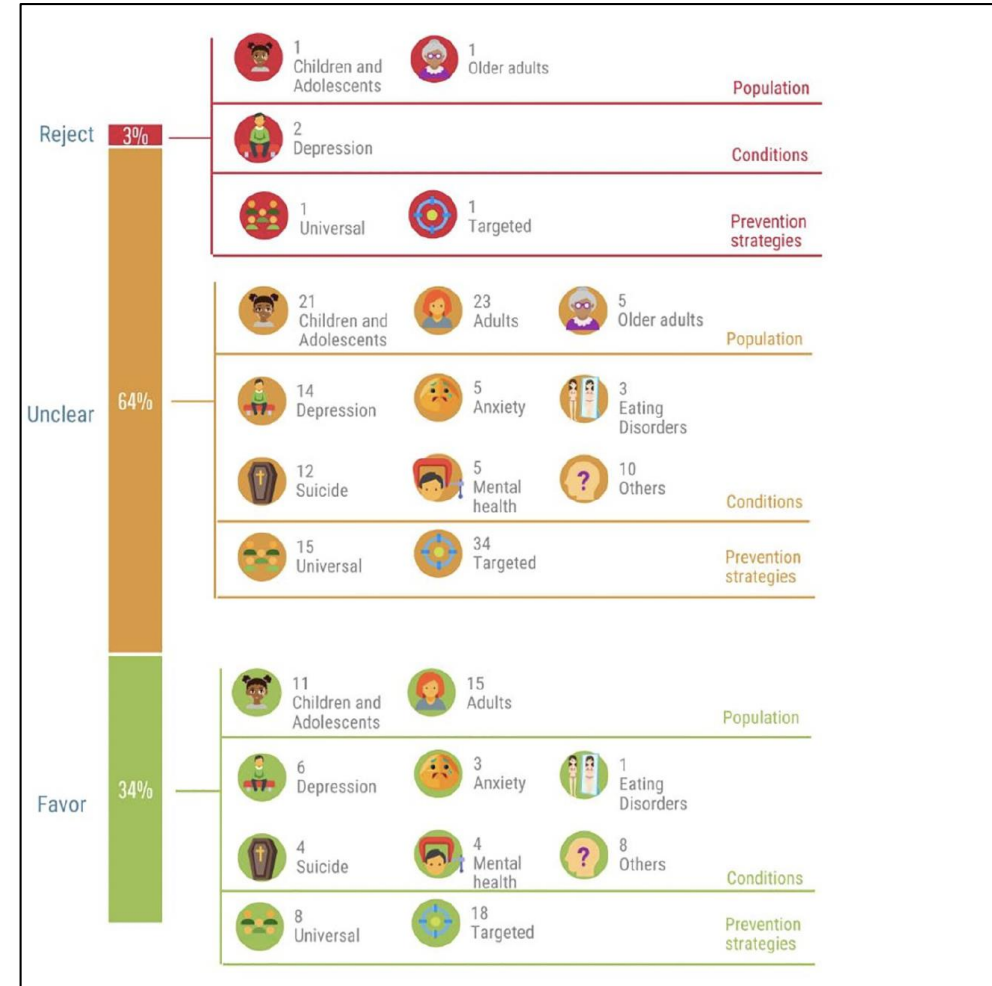
Evidence that the prevention and promotion of mental health is **cost-effective**

An analysis of 65 studies of cost-effectiveness of prevention of mental disorders and promotion of mental health showed that:

- most were cost-effective, especially targeted preventive interventions (compared to universal)
- most cost-effective in children and adolescents: screening followed by psychological interventions at school
- parenting interventions and workplace interventions were cost-effective for mental health promotion

Limitations:

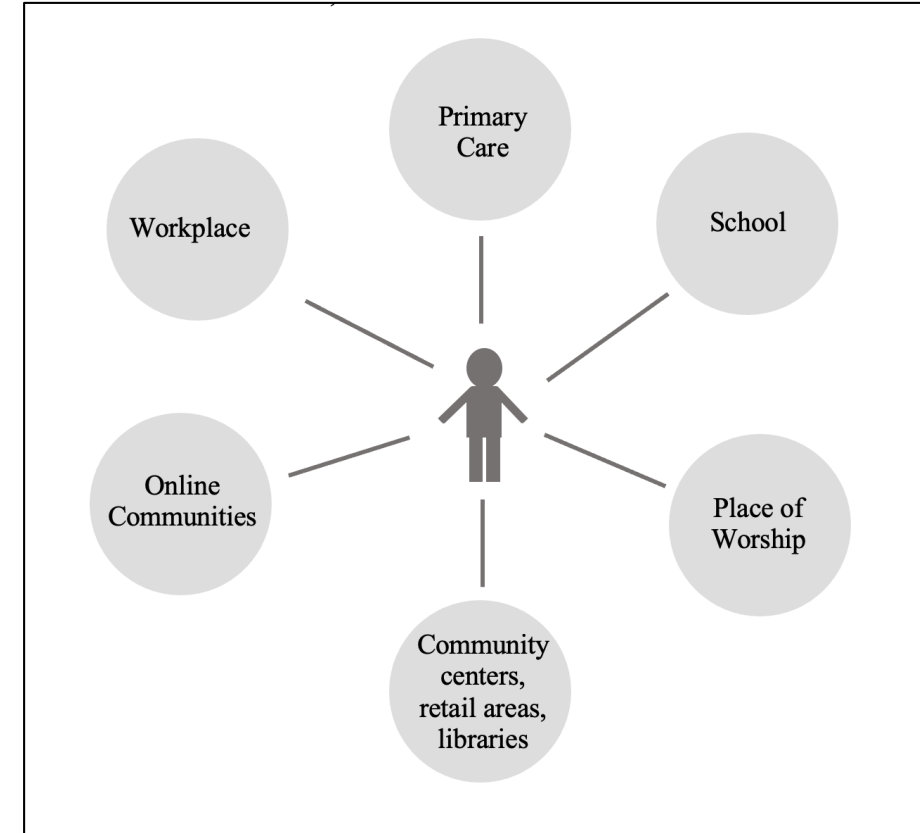
- Most of the analyses used clinical trial data, not “real world” data
- Follow-up periods were not long (typically a year)



Le et al, PLOS Med 2021

Ongoing and future directions

- **Digital** preventive interventions: Smart phone applications, virtual reality, Just-In-Time
- Integration with **community mental health programs, primary care, school programs, “task-shifting” to non-clinicians**
- **Precision medicine, targeted** approaches focused on at-risk populations identified using quantitative screening techniques, including Electronic Health Records, passive sensing data, online behavior, bio/neural markers
- Clinical trials using novel **transdiagnostic** risk signatures and outcomes



Holt & DeTore, Psych Annals 2021

Questions?