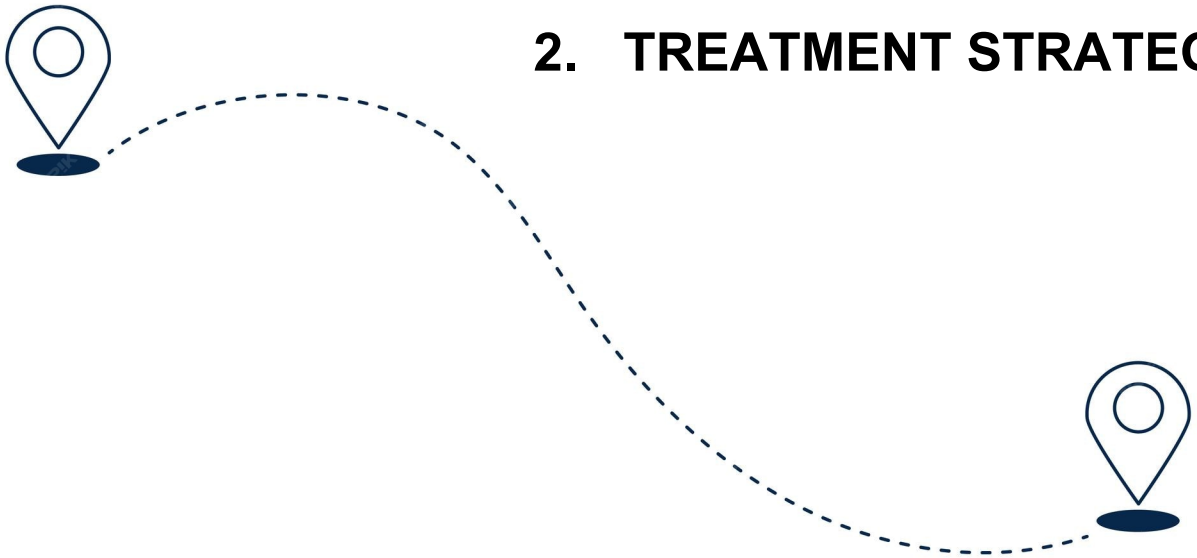
ASSIA RICCIONI

Dagli stati mentali a rischio alle Psicosi ad esordio precoce

FOCUS ON:

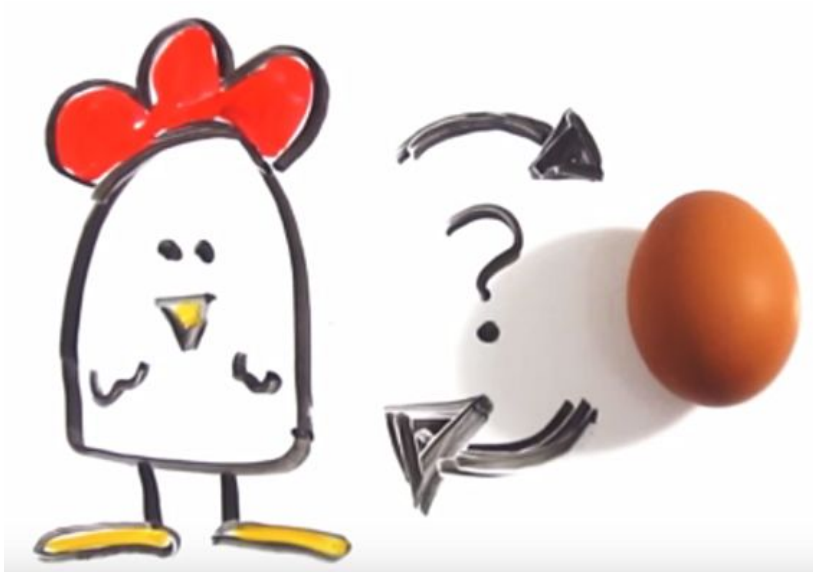
1. CO-OCCUURENT CONDITIONS □ AUTISM
2. TREATMENT STRATEGIES



ISSUES FOR CHR-P DETECTION:

- The majority of individuals with CHR-P have other **co-occurrent psychiatric conditions**;
- It is unclear if CHR-P represents **a trait or state vulnerability;**
- **It is unclear if the distress/disability is related to CHR-P or to concomitant psychopathological condition.**

Overall, findings on comorbidity suggest that in a fraction of adolescents, CHR-P states are part of **a complex clinical pictures**



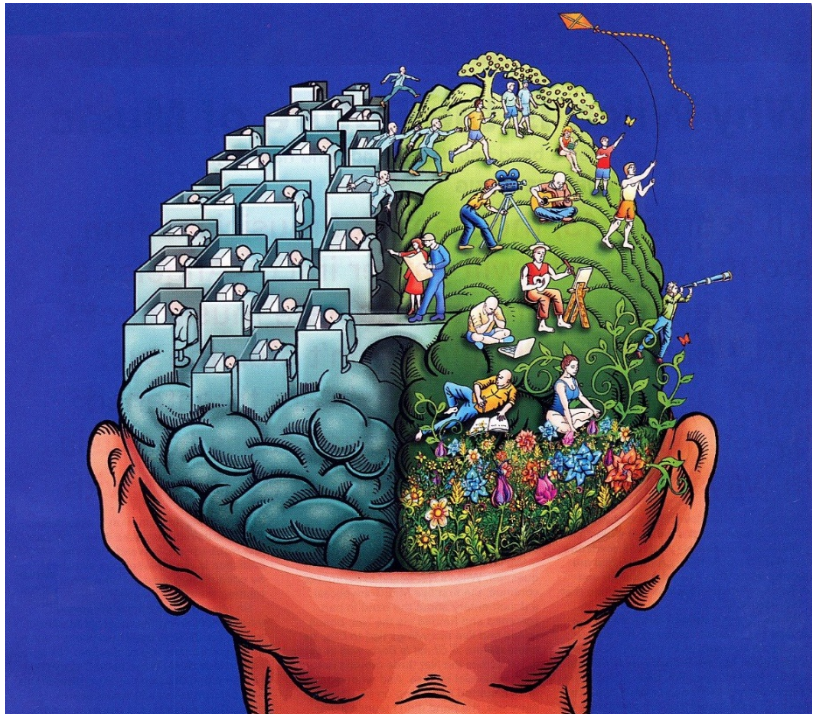
- Mood disorder (46%),
- Anxiety disorders (31%),
- ADHD (22%),
- Bipolar disorder (19%),
- **ASD (14%).**

Raballo A, Poletti M, Preti A. Editorial Perspective: Psychosis risk in adolescence - outcomes, comorbidity, and antipsychotics. J Child Psychol Psychiatry. 2022 Feb;63(2):241-244. doi: 10.1111/jcpp.13438.

EARLY DETECTION

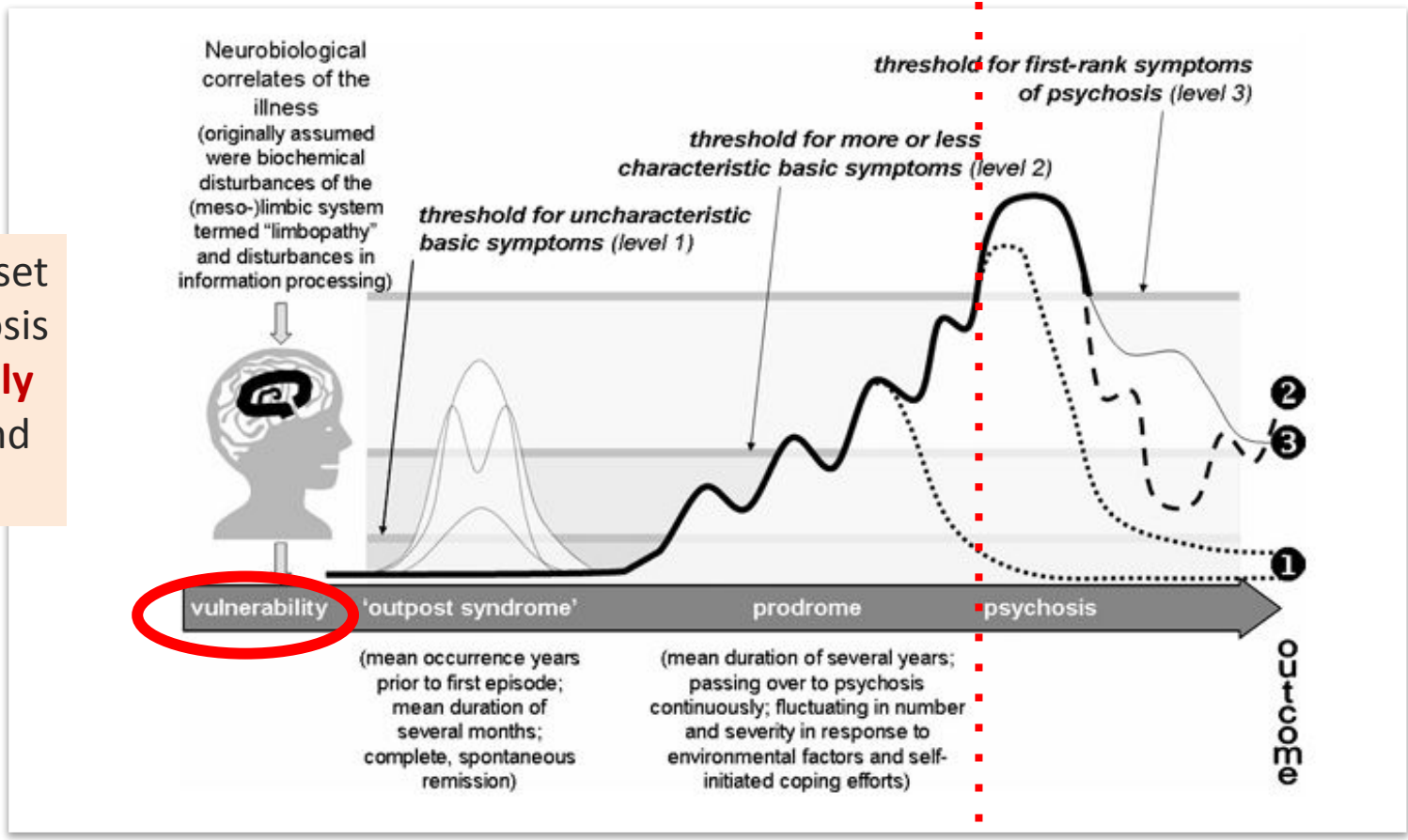
CHANGES IN DEVELOPMENTAL TRAJECTORIES?

Early identification of people in the earliest phases of psychotic disorders combined with optimal treatment is likely to **reduce the burden of disease**



EARLY INTERVENTION

Putative model of the onset and progression of psychosis in relation to **non-purely genetic risk factors** and **developmental processes**.



Frauke Schultze-Lutter; Schizophr Bull, Volume 35, Issue 1, January 2009,

Schizophrenia Research 224 (2020) 170–172

Contents lists available at ScienceDirect

Schizophrenia Research

Letter to the Editor

Neurodevelopmental predictors of conversion to schizophrenia and other psychotic disorders in adolescence and young adulthood in clinical high risk individuals

- Psychosis is associated **with a trajectory of abnormal development** (Kahn et al., 2015),wherein subtle behavioral abnormalities emerge before well-defined psychotic symptoms (Courvoisie et al., 2001; Millan et al., 2016).

- However, the relationship between neurodevelopmental and psychotic disorders remains poorly understood.

PSYCHOSIS AND AUTISM:
AN HISTORICAL ISSUE

INCREASED RATES OF CO-OCCURENCE

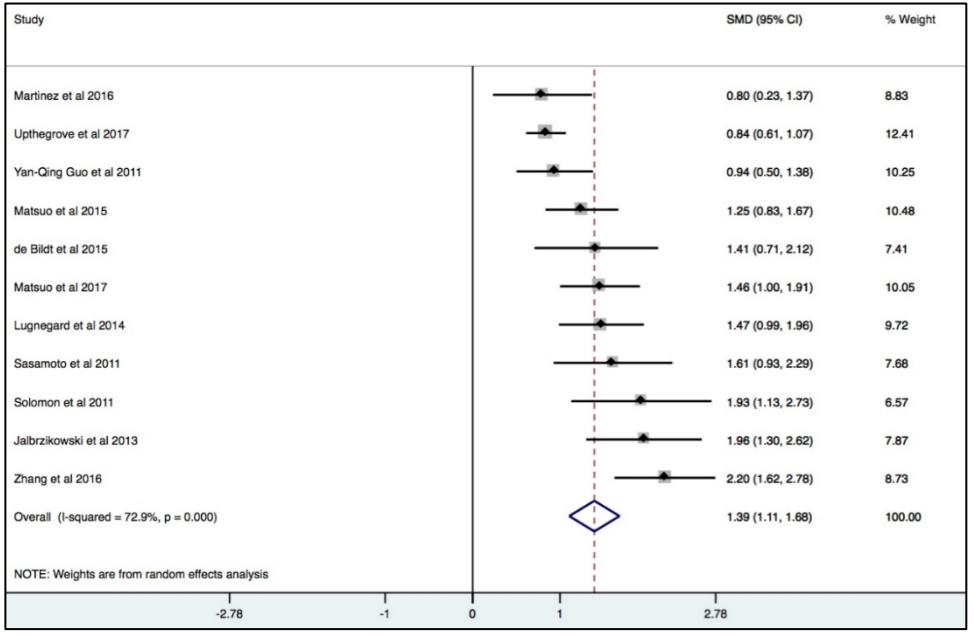
IN AUTISM

Psychiatric	
Anxiety	42–56%
Depression	12–70%
Obsessive-compulsive disorder	7–24%
Psychotic disorders	12–17%
Substance use disorders	≤16%
Oppositional defiant disorder	16–28%
Eating disorders	4–5%

Lai et al, Lancet 2014; 383: 896–910

Autistic Symptoms in Schizophrenia Spectrum Disorders: A Systematic Review and Meta-Analysis

Franco De Crescenzo [1,2,3†], Valentina Postorino [4,5†], Martina Siracusano [6,7], Assia Riccioni [8], Marco Armando [9], Paolo Curatolo [8] and Luigi Mazzone [8]*



More autistic symptoms in schizophrenia

Childhood schizotypal features vs. high-functioning autism spectrum disorder: Developmental overlaps and phenomenological differences

Michele Poletti [a,*], Andrea Raballo [b]

Schizophr Res Sep 2020

Overall, ASD and SSD have different prototypical onset timelines (i.e. respectively in early years of life and in adolescence or early adulthood) (Lai et al., 2014; Rapoport et al., 2012) and their diagnostic differentiation is possible and clinically useful in accordance with current diagnostic systems. Despite the apparently clear categorical differentiation, there is nonetheless a diagnostic grey-zone during developmental years. Indeed, during childhood and adolescence, overlapping clinical features related to social impairment and oddity could impact on the differential diagnosis between childhood schizotypal features (indexing potential developmental precursors and risk factors for SSD) and high-functioning ASD. This paper 1) offers a focused review on possible over-

Table 2
Key features for differential diagnosis.

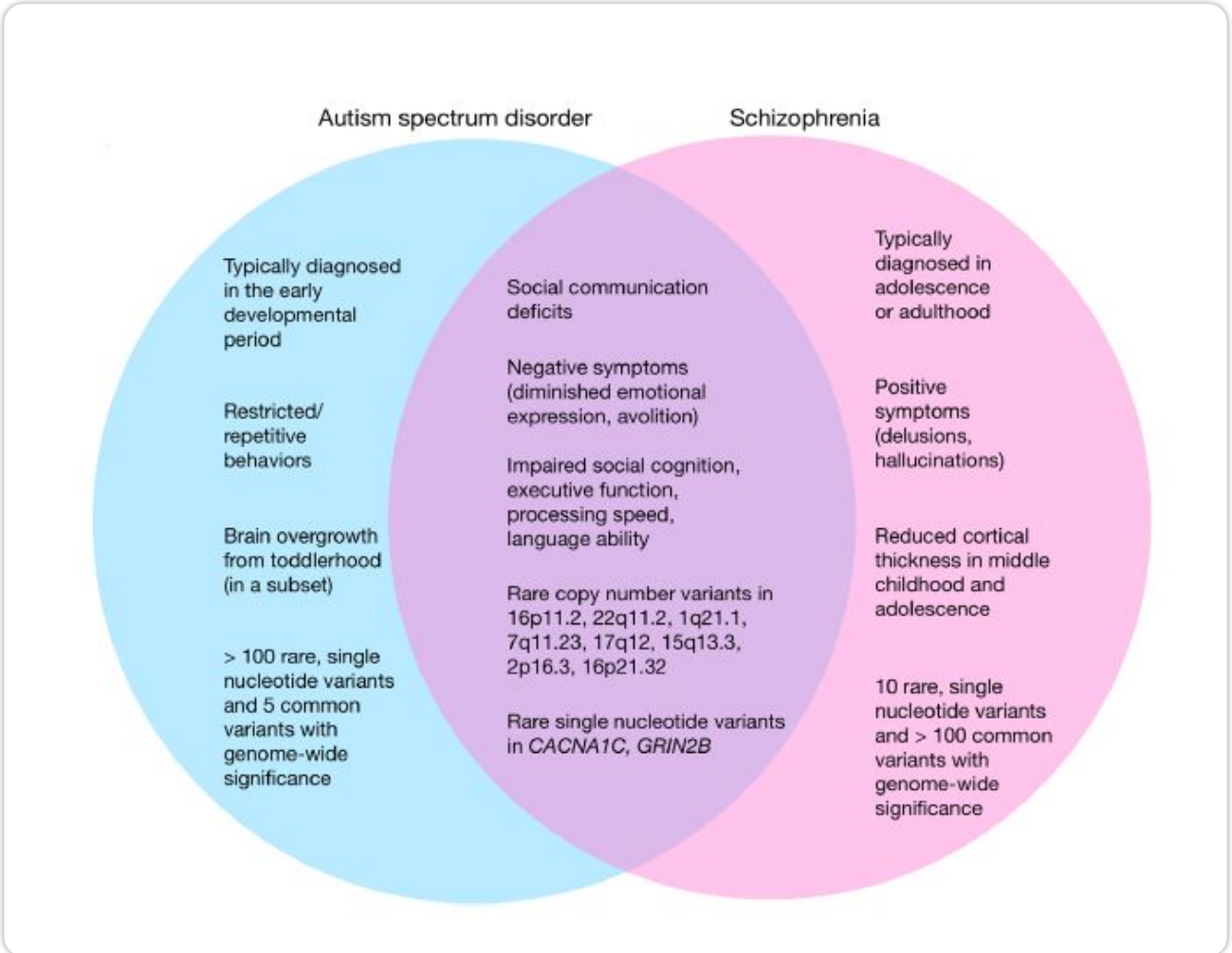
Areas of surface-level phenotypic overlap	Childhood schizotypal features	High-functioning autism spectrum disorder
Oddity (oversensitivity to feelings, extreme fantasy, daydreaming, odd thoughts and behaviors)	Perceiving, thinking and behaving toward an excessive investment in fantasy, daydreaming and detachment from reality, associated with weak reality testing and a solipsistic coloring; e.g. frequent imaginary companions.	Perceiving, thinking and behaving within restricted/rigid/stereotyped manners, associated with possible areas of hyper-competence in some specific domains; e.g. scarce investment on imaginary companions.
Social impairment (social withdrawal, social anhedonia, flattened affect, reduced emotional expressiveness)	Reflect pervasive difficulties in grasping the implicit social rules of interaction with peers; progressive subjective resonance in relation to the Self (emergence of Self-disorders); subtle feeling of alterity and alienation from peers, hard to properly verbalize, so that it can be expressed through the appearance of childhood fantasies	Reflect pervasive difficulties in grasping the implicit social rules of interaction with peers: absence of a significant subjective resonance in relation to the self

Convergent and divergent features between ASD and SSDs

CLINICAL FEATURES

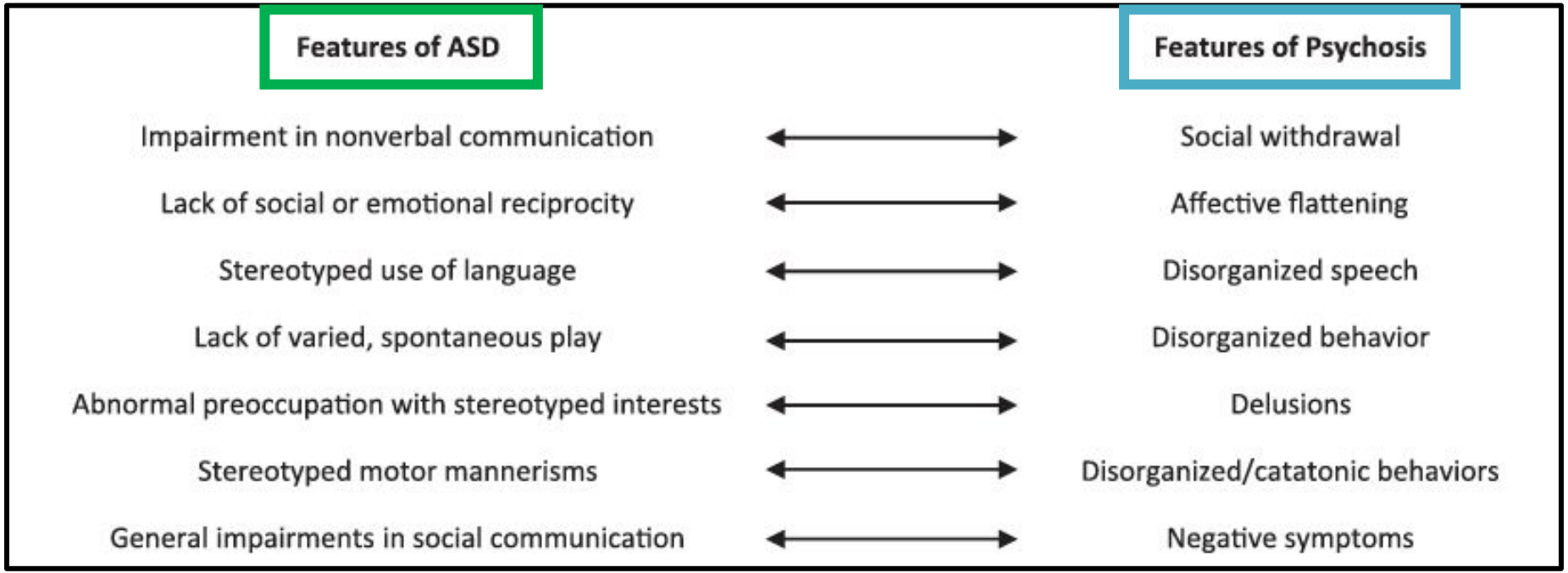
NEUROANATOMY

GENETICS



Jutla et al 2022

CLINICAL FEATURES



Cochran et al; Child Adolesc Psychiatric Clin N Am 22 (2013).

frontiers in Psychiatry

REVIEW
published: 28 February 2022
doi: 10.3389/fpsyt.2022.768586

Recognizing Psychosis in Autism Spectrum Disorder

Michele Ribolsi[1], Federico Fiori Nastro[2,3], Martina Pelle[2,3], Caterina Medici[2,3], Silvia Sacchetto[2,3], Giulia Lisi[4], Assia Riccioni[5], Martina Siracusano[6], Luigi Mazzone[5] and Giorgio Di Lorenzo[2,3,7]*

- The **detection of the psychotic symptoms** has proven to be particularly challenging in individuals with Autism, **especially at prodromal phases.**

- To note, **social skills impairment** has been identified as a significant predictor of conversion to full psychosis in individuals considered at "**clinical high risk" (CHR)** for psychosis.

PubMed®

autism AND attenuated psychosis AND clnical risk psychosis

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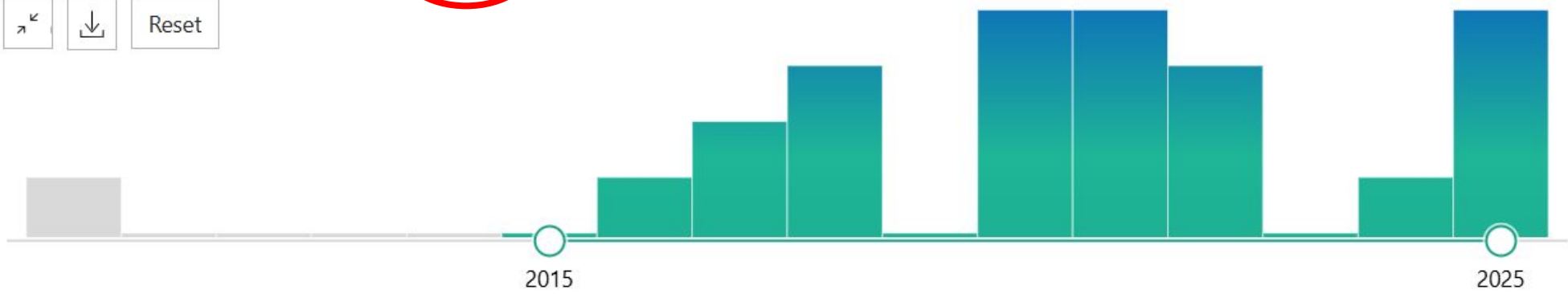
RESULTS BY YEAR

18 results

Page 1 of 2

Reset



autismo
"Autismo Tor Vergata"

OUR RESEARCH PROJECT

PTV
FONDAZIONE PTV
POLICLINICO TOR VERGATA

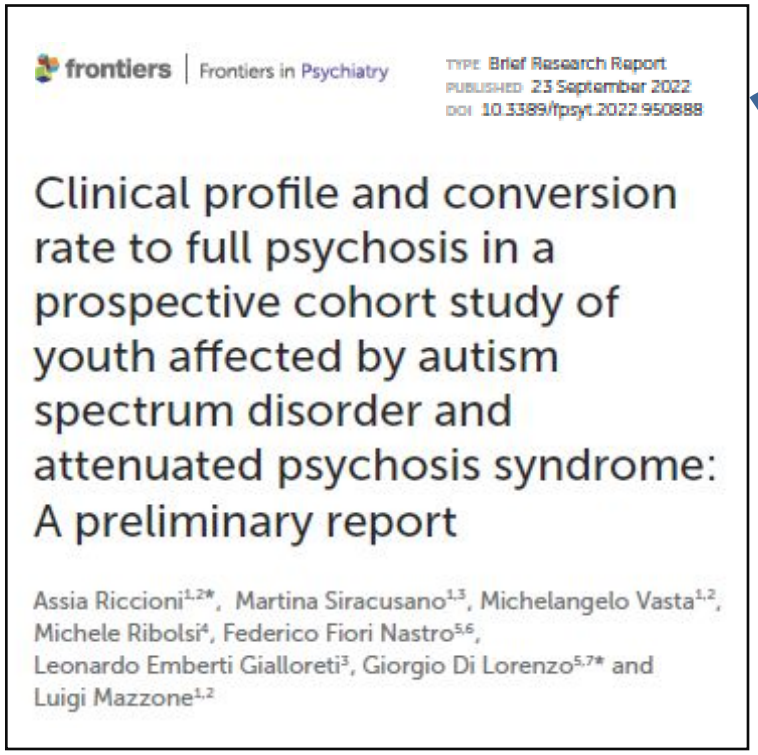
Università di Roma
Tor Vergata

A **prospective cohort study** aimed to characterize, from a clinical and neurophysiological point of view, a sample of ASD individuals (age range: **9–23** years) with or without concomitant APS (ASD *vs* ASD/APS).

Networking with

Bambino Gesù
OSPEDALE PEDIATRICO

STUDY 1



frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 23 September 2022
DOI 10.3389/fpsyt.2022.950888

Clinical profile and conversion rate to full psychosis in a prospective cohort study of youth affected by autism spectrum disorder and attenuated psychosis syndrome: A preliminary report

Assia Riccioni[1,2*], Martina Siracusano[1,3], Michelangelo Vasta[1,2], Michele Ribolsi[4], Federico Fiori Nastro[5,6], Leonardo Emberti Gialloreti[3], Giorgio Di Lorenzo[5,7*] and Luigi Mazzone[1,2]

ASD *vs* ASD/APS

- We longitudinally evaluate a sample of young ASD individuals (age, mean ± *SD*: 13 ± 2.9) with (**ASD/APS *n* = 13**) or without (**ASD *n* = 18**) concomitant APS through a standardized assessment of autistic (Autism Diagnostic Observation Schedule–Second Edition; ADOS−2) and psychotic (Structured Interview for Psychosis-Risk Syndromes, SIPS) symptoms and cognitive and adaptive skills;

- We estimated the **conversion rate** to full psychosis (according to SIPS criteria) over time (39.6 ± 11.5months) and **explored the role of clinical variables** at baseline in the transition to full psychosis.

Baseline (T0) clinical profiles characteristics

RESULTS

	ASD (n = 18) MEAN (SD)	ASD/APS (n = 13) MEAN (SD)	*p*	*t*	*Cohen's d*
Age T0	12.5 (2.91)	13.6 (3.12)	0.290	1.07	0.364
Male/Female	15/ 3	9/ 4	-	-	-
IQ	105.5 (19.5)	98 (20.1)	0.307	1.04	0.378
ABAS-II					
ABAS_GAC	78.28 (19.3)	63.54 (13.2)	0.024	2.530	0.891
ABAS_CAD	85.22 (17.4)	71.92 (13.8)	0.030	2.280	0.846
ABAS_SAD	80.67 (18.1)	68.08 (10.9)	0.034	2.225	0.842
ABAS_PAD	77.11 (21.6)	60.54 (15.9)	0.027	2.334	0.873
ADOS-2					
ADOS_SA	7.67 (2.3)	9.54 (3.1)	0.686	0.164	0.685
ADOS_RRB	1.83 (1.5)	2.23 (2.0)	0.326	0.966	0.226
ADOS_CSS	5.83 (1.6)	6.85 (2.1)	0.119	2.42	0.546
SRS					
SRS_T	73.61 (15.7)	81.36 (15.6)	0.207	−7.753	0.495
SRS_SA	59.89 (14.3)	70.82 (13.4)	0.051	−2.044	0.776
SRS_SC	67.94 (17.1)	74.64 (18.6)	0.330	−0.991	0.375
SRS_SCo	73.28 (11.9)	78.09 (15.5)	0.356	−4.813	0.348
SRS_SM	72.67 (14.7)	73.73 (19.2)	0.868	−1.061	0.061
SRS_AM	75.11 (16.4)	81.36 (14.9)	0.313	−6.253	0.398
SIPS					
SIPS-P	2.67 (1.53)	6.62 (2.3)	<0.001	17.29	2.02
SIPS-N	2.39 (1.57)	5.38 (4.2)	0.291	1.11	0.943
SIPS-D	1.28 (1.48)	4.00 (2.8)	<0.001	11.49	1.21
SIPS-G	1.96 (1.05)	2.92 (2.6)	0.119	2.42	0.484
SIPS-Total	7.39 (3.61)	18.85 (9.7)	<0.001	23.88	1.56

No statistically significant differences in terms of age and IQ

The ASD/APS group presented:

- More severe impairment in the adaptive functioning profile (**ABAS-II scores**);
- Higher **SRS** social awareness (**SA**) and social cognition (**SC**) scores; even if not a statistically significant level, a quite large effect size came out in the SA domain (d = 0.78);
- Subthreshold differences within the **ADOS-2** scores;
- Greater scores in the total SIPS, SIPS-P and SIPS-D with **no significant differences in SIPS-N and SIPS-G**;

STUDY 1

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 11 June 2020
doi: 10.3389/fpsyt.2020.00548

Autism Spectrum Disorder and Schizophrenia Are Better Differentiated by Positive Symptoms Than Negative Symptoms

Dominic A. Trevisan[1], Jennifer H. Foss-Feig[2,3], Adam J. Naples[1], Vinod Srihari[4], Alan Anticevic[4] and James C. McPartland[1]**

REVIEW
published: 28 February 2022
doi: 10.3389/fpsyt.2022.768586

Recognizing Psychosis in Autism Spectrum Disorder

Michele Ribolsi[1], Federico Fiori Nastro[2,3], Martina Pelle[2,3], Caterina Medici[2,3], Silvia Sacchetto[2,3], Giulia Lisi[4], Assia Riccioni[5], Martina Siracusano[6], Luigi Mazzone[5] and Giorgio Di Lorenzo[2,3,7]*

- A growing body of evidence starts to support the knowledge that **symptoms overlap between autism and psychosis is more prominent among negative symptoms;**
- Whereas **positive symptoms (RRBs/delusion)** are more disorder specific .
- Hypothesis for potential reduced reliability of available tools (i.e., SIPS/SOPS) in the detection of negative symptomatology in the ASD population;

RESULTS **Follow-up (T1) conversion rate to psychosis**

Our result are quite discordant with an available meta-analysis by *Vaquerizo-Serrano et al. (2022)* showing a conversion rates at **2 years**, ranging from **15.4 to 18.2%**.

- **Conversion rate was 30.7% (mean T0-T1 difference: 3 years)**

Meta-Analysis > Eur Psychiatry. 2015 Mar;30(3):405-16. doi: 10.1016/j.eurpsy.2015.01.010. Epub 2015 Feb 27.

EPA guidance on the early detection of clinical high risk states of psychoses

F Schultze-Lutter [1], C Michel [1], S J Schmidt [1], B G Schimmelmann [1], N P Maric [2], R K R Salokangas [3], A Riecher-Rössler [4], M van der Gaag [5], M Nordentoft [6], A Raballo [7], A Meneghelli [8], M Marshall [9], A Morrison [10], S Ruhrmann [11], J Klosterkötter [12]

Being in line with other researches on the **CHR-P population** showing a conversion rate of **25–35%** when considering a follow-up time frame of **3 years.**

RESULTS

Follow-up (T1) conversion rate and clinical baseline variables

	ASD/APS− (n = 9; 69%) MEAN (SD)	ASD/APS+ (n = 4; 31%) MEAN (SD)	*p*	*t*	*Cohen's d*
Age T1	13.2 (1.3)	14.5 (5.6)	0.520	−0.665	0.319
Baseline characteristics					
IQ	106.5 (18.1)	78.7 (6.4)	0.014	2.926	2.047
ABAS-II					
ABAS_GAC	66.9 (11.1)	56.0 (16.1)	0.178	1.440	0.788
ABAS_CAD	74.5 (13.2)	66.0 (15.5)	0.326	1.028	0.590
ABAS_SAD	71.6 (10.5)	60.0 (7.7)	0.074	1.974	1.259
ABAS_PAD	62.4 (15.7)	56.2 (17.9)	0.542	0.629	0.368
SIPS					
SIPS-P	6.1 (1.7)	4.7 (1.5)	0.237	10.5	0.873
SIPS-N	3.2 (2.2)	4.7 (1.3)	0.099	28.5	0.830
SIPS-D	2.6 (0.7)	3.0 (1.4)	0.418	23.0	0.361
SIPS-G	2.2 (0.9)	1.5 (1.0)	0.195	10.0	0.735
SIPS Total	14.2 (2.2)	14.0 (2.5)	0.873	17.0	0.084
ADOS-2					
ADOS_SA	9.2 (2.2)	10.2 (5.1)	0.606	−0.531	0.254
ADOS_RRB	2.1 (2.1)	2.5 (1.9)	0.762	−0.310	0.194
ADOS_CSS	6.6 (2.1)	7.2 (2.4)	0.660	−0.452	0.266

- No statistically significant association emerged between the severity of autistic and psychotic symptoms at baseline and subsequent conversion to psychosis.
- Notably, the **ASD/APS+** group showed greater impairment in adaptive functioning (**ABAS-II GAC**), particularly in the **social domain** (**ABAS-II SAD**).
- Moreover, individuals with ASD/APS who exhibited **lower IQ** scores at T0 were more likely to later convert to full psychosis (large effect size, d = 2.05).

Legend:
ASD/APS- = non converter
ASD/APS+ = converter

A recent meta-analysis reported that **CHR individuals exhibit greater cognitive impairment** compared to healthy controls (Millman et al., 2022); however, **it remains unclear whether significant differences exist between converters and non-converters** (Addington et al., 2012).

TO SUM UP:

- Our findings start to provide a more informative characterization of the ASD sub-phenotype by a **dimensional approach** within individuals considered "at-risk" for developing psychotic disorders.

- Our preliminary findings revealed that nearly a third of young individuals with ASD/APS convert to full psychosis over time.

- To note, conversion to full psychosis was not affected by the severity of the autistic and psychotic symptoms, but by decreased cognitive and adaptive skills.

STRENGHTS

- The clinical assessment through standardized tools performed by a multidisciplinary team of expert clinicians in the fields of both, autism and psychosis.
- The inclusion of ASD individuals with a wide age range (9–23 years) allowing us to assess the presence of psychosis risk at a very early prodromal phase and during the young-adult age.

LIMITATIONS

- The relatively small sample size and its limited statistical power.
- The inclusion of "selected" individuals with ASD (without neuropsychiatric comorbidities except APS) could have contributed to a possible recruitment bias.
- Lack of a control group of individuals with APS without ASD which not allowed us to clarify differences in the phenomenology of psychotic symptoms between ASD and non ASD individuals

TO BE CONTINUED…

STUDY 2

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TYPE Original Research
PUBLISHED 31 March 2025
DOI 10.3389/fpsyt.2025.1536361

Investigating the attenuated psychosis syndrome in youth with autism spectrum disorder: results from an observational study

Assia Riccioni[1*†], Maria Pontillo[2†], Lenardo Emberti Gialloreti[3], Mariagrazia Cicala[3], Michelangelo Vasta[4,5], Mattia Gatto[1,4], Lucrezia Arturi[4], Martina Siracusano[1,3], Michelangelo Di Luzio[2], Stefano Vicari[2,6‡] and Luigi Mazzone[1,4‡]

ASD *vs* ASD/APS *vs* APS

UO Neuropsichiatria Infantile
Prof. Luigi Mazzone
Dr. Assia Riccioni

UO Neuropsichiatria Infantile
Prof. Stefano Vicari
Dr. Maria Pontillo

AIM

To characterize the clinical phenotype of a sample of young (age range 9-23 years) **ASD/APS** in comparison to individuals with **APS** and with **ASD** alone;

METHOD

A standardized assessment of autistic (Autism Diagnostic Observation Schedule–Second Edition; ADOS−2) and pre-psychotic symptoms (Structured Interview for Psychosis-Risk Syndromes, SIPS) as well as cognitive and adaptive skills.

STUDY 2

RESULTS

ASD/APS n= 48 (*M:F*= 31:17; M age 15.2)
ASD n= 30 (*M:F*= 25:5; M age 14.8)
APS n=93 (*M:F*= 47:46; M age 15.3)

No statistically significant differences emerged in terms of age (p=0.683), gender (p= 0.073), and IQ (p=0.170).

THE ASD/APS INDIVIDUALS

- Consistent with our previous study, significantly **poorer general adaptive skills** compared to both, the APS group ($p = 0.006$) and the ASD group ($p = 0.005$).
- Significantly **higher scores in the repetitive and restricted behavior (RRBs)** domain compared to the ASD group ($p < 0.001$).
- Compared to the APS group, exhibited **lower scores across all SIPS domains**, with **the exception of SIPS-P1** (*unusual thought content/delusional ideas*; $p = 0.062$; $t = -1.882$; $F = 5.44$) and **SIPS-P3** (*grandiosity*; $p = 0.156$;$t = -1.435$; $F = 22.6$).

Scan me to read more

- Being in line, the ASD/APS group reached a **mean SIPS-P score ≥3 (thus confirming the presence of an APS condition) only in the P1 item** (*unusual thought content/delusion ideas*; 3.1 ± 0.9).

	SIPS-P				
	P1	P2	P3	P4	P5
	(N)%	*(N)%*	*(N)%*	*(N)%*	*(N)%*
ASD/APS	(39) 81.2	(29) 60.4	(18) 37.5	(26) 54.2	(24) 50
APS	(85) 91.3	(86) 92.5	(34) 36.5	(81) 87	(79) 85

Based on the SIPS/SOPS criteria, the presence of APS is confirmed when a score of 3, 4, or 5 on the SIPS positive symptoms scale (SIPS-P) is reached.
SIPS, Structured Interview for Psychosis-Risk Syndromes; SIPS-P, positive symptoms domain; P1, unusual thought content; P2, suspiciousness; P3, grandiosity; P4, perceptual abnormalities; P5, disorganized communication.

- To note, in ASD individuals could be particularly challenging to distinguish between psychotic features—such as **delusional beliefs and disorganized speech**—and ASD core symptoms particularly referred to **RRBs**, which include stereotyped languages or restricted interests;

- Along this, ASD/APS individuals included in our sample showed greater scores in the terms of RRBs in comparison with ASD.

- We could therefore **hypothesize that ASD individuals who presented greater symptoms severity in terms of RRBs could be the one at increased risk for APS, specifically detected by a higher score in the SIPS-P 1 item**;

STUDY 2

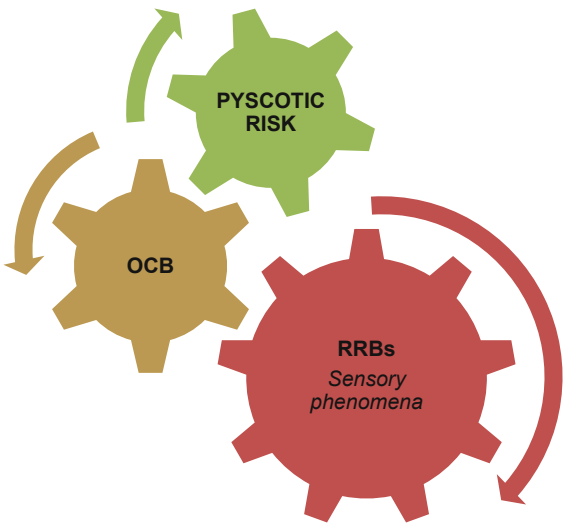
RRBs and PSYCHOTIC RISK

Schizophr Res. 2020 Oct:224:170-172. doi: 10.1016/j.schres.2020.10.008. Epub 2020 Nov 2.

Neurodevelopmental predictors of conversion to schizophrenia and other psychotic disorders in adolescence and young adulthood in clinical high risk individuals

Amandeep Jutla [1], Allegra Califano [2], Gabriella Dishy [2], Hannah Hesson [2], Leda Kennedy [2], Brooke Lundgren [2], Tyler Pia [2], Jeremy Veenstra-VanderWeele [2], Gary Brucato [2], Ragy R Girgis [2]

Jutla et al. recently investigated whether **previous neurodevelopmental symptoms** could predict that an individual at CHR will convert to psychosis in a sample of n=151 CHR cohort, showing that **RRBs during childhood increase the risk of later conversion** **(OR 13.29, 95% CI 1.5–309.84).**



Consistent with a **transdiagnostic perspective**, available studies have highlighted a **neurodevelopmental phenomenological bottom-up model**, suggesting that a history of neurodevelopmental RRBs, particularly those related to **sensory phenomena**, may precede the emergence of obsessive-compulsive behaviors, well recognized as a risk factor for psychosis

No statistically significant differences came out in terms of age onset for the APS condition between ASD/APS (13.5 ± 2.0) **and the APS individuals** (13.3 ± 2.2) (F=0.253; p=0.601).

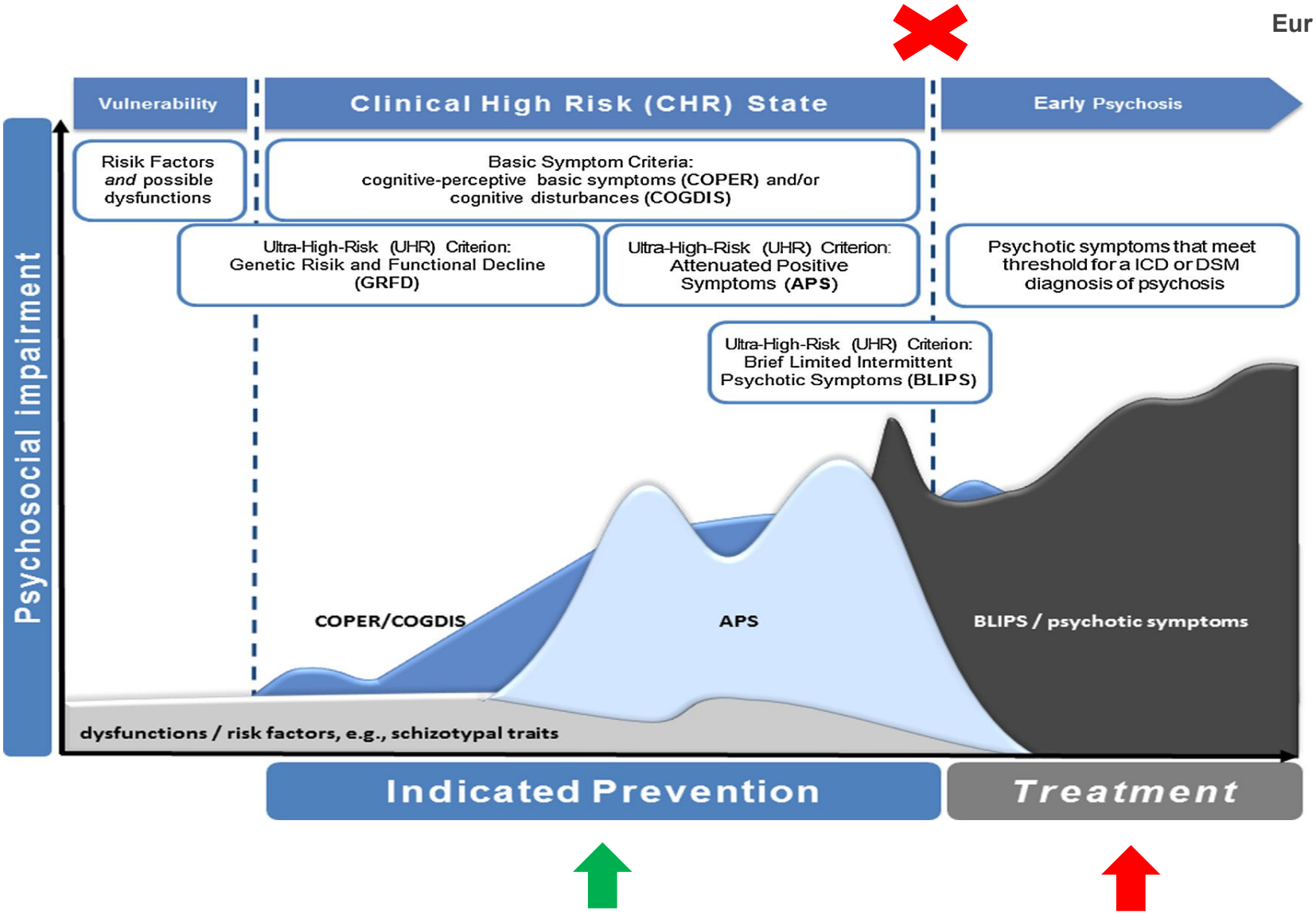
- ❑ Emphasize the **importance of screening for APS in ASD**, particularly those considered at increased risk.
- ❑ Early detection and intervention could facilitate timely **therapeutic support**, potentially improving long-term outcomes for these individuals.

ULTRA HIGH RISK PSYCHOSIS

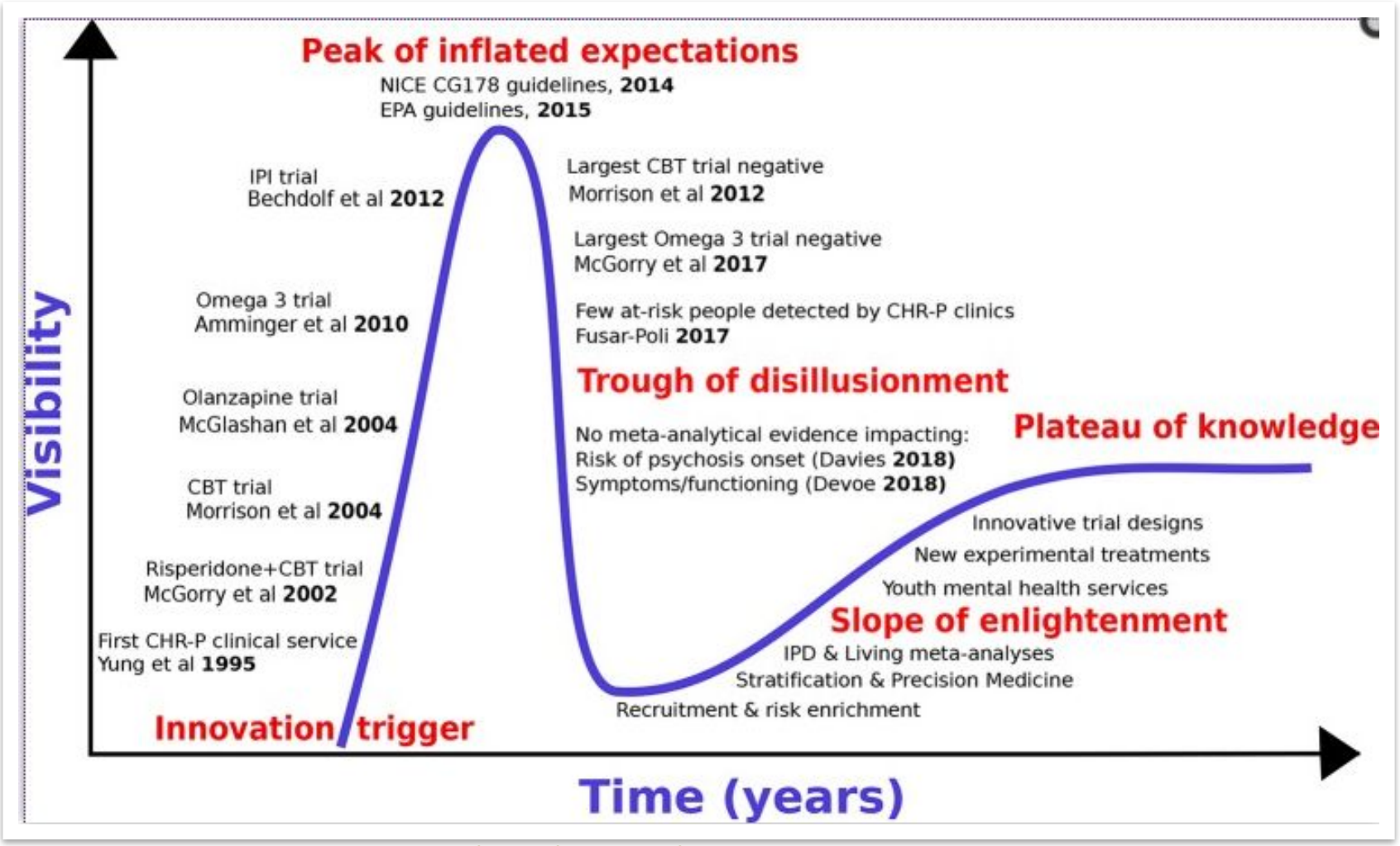
TO TREAT OR NOT TO TREAT, THAT IS THE QUESTION

MEDICAL SCHOOL
CLINICAL SERVICE
Child Neuropsychiatry
University of Rome Tor Vergata

Eur Psychiatry, 2015



“The hype cycle of preventive treatments for psychosis”



Fusar-Poli P et al Front Psychiatry. 2019 Dec 11;10:764.

WHAT DO WE KNOW

BRITISH JOURNAL OF PSYCHIATRY (2005), 187 (suppl. 48), s120–s124

International clinical practice guidelines for early psychosis

INTERNATIONAL EARLY PSYCHOSIS ASSOCIATION WRITING GROUP[1]

- Pharmacological treatment **should be** introduced with great care in drug-naive patients;
- **Use of the minimum effective dose** of atypical or second generation antipsychotics wherever possible;
- **Psychosocial interventions** have a crucial role in early treatment.

Choice of AP in FEP

- Response to lower doses of AP in FEP but also **increased sensitivity to side effects**;
- **No superiority of one AP over another;**
- Avoid typical AP (e.g., haloperidol), risk of extrapyramidal side effects;

- **Give preference to:**
  - Aripiprazole (>13 FDA)
  - Lurasidone (>13 FDA)
  - Brexpiprazole (>13 FDA)
  - Cariprazine (>18 FDA; some evidence for safety under 18)
  - Amisulpride (no FDA approval; no evidence for safety under 18)

- **Higher risk of weight gain/metabolic syndrome with:**
  - Quetiapine
  - Risperidone
  - Olanzapine

AGENZIA ITALIANA DEL FARMACO

«CURRENT» SITUATION

		AGE
AP	**ARIPRIPAZOLO**	> 15 aa
	PERICIAZINA	> 12 aa
	LURASIDONE	>13 aa
	CLOZAPINA	> 16 aa

…AND WHAT ABOUT THE PRE-PSYCHOTIC PERIOD?

"If young people with an at-risk mental state are actively seeking help for the distress and disability associated with their symptoms, they need to be:

1. engaged and assessed;
2. offered **regular monitoring** of mental state and offered support;
3. offered **specific treatment for associated symptoms** (ie. depression, anxiety)
4. provided with **psychoeducation**;
5. offered **family** education and support;

The evidence of effectiveness of pharmacological treatment aimed to reduce the risk of transition psychosis remains unclear.

Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (ShangHai At Risk for Psychosis)

Australian & New Zealand Journal of Psychiatry
2020, Vol. 54(7) 696–706
DOI: 10.1177/0004867420917449

TianHong Zhang[1], LiHua Xu[1], XiaoChen Tang[1], YanYan Wei[1], Qiang Hu[1], YeGang Hu[1], HuiRu Cui[1], YingYing Tang[1], Li Hui[2], ChunBo Li[1], LiPing Cao[3], Zheng Lu[4] and JiJun Wang[1,5,6]

Editor's Choice

Longitudinal data on 450 CHR-P individuals (age range 13-45 y) followed up for 3 years

- Overall, the **24%** (n=108) experienced a transition to psychosis;
- CHR-P subjects **who did not received AP showed a lower transition rate** (17.7% ***vs*** 26.9%);
- AP treatment was associated with a higher rate of transition to psychosis **in mild CHR cases** (i.e. SIPS total positive score >10);
- Among patients on AP, **monotherapy or low-dose treatment** was associated with lower transition rates;

WARNING

Antipsychotic treatment in clinical high risk for psychosis: Protective, iatrogenic or further risk flag?

Australian & New Zealand Journal of Psychiatry
2021, Vol. 55(5) 442–444
DOI: 10.1177/0004867420984836

Andrea Raballo[1,2], Michele Poletti[3] and Antonio Preti[4]

- **Major guidelines (e.g. NICE, EPA, RANZCP): AP should not be considered as the first-line intervention for psyhcosis prevention;**

- Authors also **suggest not to treat mild CHR individuals with AP**, since such exposure could have a *negative prognostic impact* on transition risk.

THE AP PARADOX

How should we consider AP as harmful and not effective in CHR-P states and – at the same time – beneficial in more severe ones (such as FEP and chronic psychosis)?

HOW CAN WE DEAL WITH IT?

Raballo A et al 2021

HOW CAN WE DEAL WITH IT?

- A well-pondered evaluation of **causality between clinical severity and AP** prescription in clinical settings;
- Indeed, the prescription of AP it is **not an evidence-based** primary treatment choice in CHR states, **but a need-based**, motivated by the perception of increasing clinical severity.
- Consequently, such increasing severity could plausibly increase the risk of symptomatically transition to psychosis despite the pharmacologic prescription itself.

Antipsychotic prescription in CHR: **risk signal rather than iatrogenic factor?**

Raballo A et al 2021

JAMA Psychiatry | Brief Report

Baseline Antipsychotic Dose and Transition to Psychosis in Individuals at Clinical High Risk

A Systematic Review and Meta-Analysis

Andrea Raballo, MD, PhD; Michele Poletti, PsyD; Antonio Preti, MD

To test whether the negative prognostic effect of baseline antipsychotic exposure in individuals at CHR-P follows a **dose-effect pattern**.

- N=8 studies were included in the SR and MA encompassing **n=290 CHR-P** (Age, 19.4±2.6 years) **who were exposed to AP at baseline**;
- 22.7% (n=66) converted to psychosis;
- **Those who converted to psychosis had higher baseline AP doses** than those who did not in both the common-effects model (Hedges g, 0.41; 95% CI, 0.12-0.70; z, 2.78; P = .005) and in the random-effects model (Hedges g, 0.41; 95% CI, 0.15-0.67; z, 3.69; P = .008; τ2, 0.0).

EUROPEAN PSYCHIATRIC ASSOCIATION

Accepted: 20 March 2025

The impact of aripiprazole on neurocognitive function in individuals at clinical high risk for psychosis: A comparison with olanzapine and non-antipsychotic treatment

JiaHui Zeng[1], Andrea Raballo[2,3], JiaYi Ye[1], YuQing Gao[1], WenJun Su[1], YanYan Wei[1], XiaoChen Tang[1], LiHua Xu[1], YeGang Hu[1], Dan Zhang[1], HuiRu Cui[1], YingYing Tang[1], XiaoHua Liu[1], HaiChun Liu[4], Tao Chen[5,6], ChunBo Li[1], JiJun Wang[1,7,8] and TianHong Zhang[1]

This study investigates the association between aripiprazole and olanzapine use and cognitive and clinical outcomes in CHR individuals, compared to those receiving no antipsychotic treatment.

A retrospective analysis was conducted on **127 participants** from the Shanghai At Risk for Psychosis (SHARP) cohort, categorized into three groups:

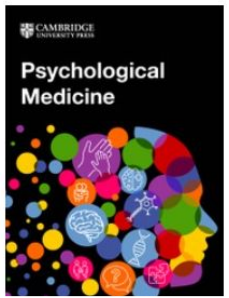
aripiprazole ***VS*** olanzapine ***VS*** no antipsychotic

- Neurocognitive performance was evaluated using the MATRICS Consensus Cognitive Battery (MCCB), while clinical symptoms were assessed through the Structured Interview for Prodromal Syndromes (SIPS) at baseline, 8 weeks, and one year.

- The non-medicated group demonstrated greater improvements in cognitive performance, clinical symptoms, and functional outcomes compared to the medicated groups.

- Among the antipsychotic groups, **aripiprazole was associated with better visual learning outcomes** than olanzapine.

- Improvements in neurocognition correlated significantly with clinical symptom relief and overall functional gains at follow-up assessments.



Baseline benzodiazepine exposure is associated with greater risk of transition in clinical high-risk for psychosis (CHR-P): a meta-analysis

Published online by Cambridge University Press: **23 August 2023**

Andrea Raballo, Michele Poletti and Antonio Preti Show author detai

N= 5 studies included;
N= 1819 individuals

- The proportion of participants exposed to BDZ at baseline ranged from 5.5% to 46.2%, with an average of **16.8%**;
- At the end of the period of observation, **28.4% participants developed psychosis** among the BDZ-exposed against 9.3% (7.3 to 11.9%) among the controls (Risk Ratio was **2.42** 95% CI 1.38-4.23);
- **CHR-P participants who were already under BDZ treatment at baseline had more than double chance of transition to psychosis than CHR-P participants who were BDZ-naïve.**

HYPOTHESIS

- Confounding by indication?
- E/I imbalance?

Meta-Analysis > Psychol Med. 2023 Jul;53(10):4550-4560. doi: 10.1017/S0033291722001428.
Epub 2022 Jun 3.

Do antidepressants prevent transition to psychosis in individuals at clinical high-risk (CHR-P)? Systematic review and meta-analysis

Andrea Raballo [1] [2], Michele Poletti [3], Antonio Preti [4]

N= 16 studies included;
N= 1819 individuals

- **26%** of the participants were already exposed to AD at baseline;
- At the end of the follow-up: 13.5% (95% CI 10.2-17.1%) of AD exposed transitioned to psychosis ***vs*** 21.0% of non-AD exposed CHR-P (*n* = 1371).
- **CHR-P participants who were under AD treatment at baseline had a lower risk of transition than non-AD exposed CHR-P (the RR was 0.71 95% CI 0.56-0.90).**

WHY?

- **Index for a mental state clinically judjed as a need for AD;**
- Therefore, it depends **on wich symptoms are clinically more prominent**


FOCUS ON SYMPTOMS!

Journal of the American Academy of Child & Adolescent Psychiatry, 2022

CLINICAL PERSPECTIVES

Beyond Diagnosis: Formulation–Storytelling and Maps

Carlos Hoyos, MRCPsych, and Samuele Cortese, MD, PhD

"Diagnosis is considered the cornerstone of modern medicine. ***In psychiatry, the concept of diagnosis has arguably helped many individuals receive effective support and treatment****. For instance, many would agree that a number of children and their families have benefited from a diagnosis of attention-deficit/hyperactivity disorder, leading to a pharmacological treatment that is the most efficacious in psychiatry, at least in the short term.*
However, diagnoses in psychiatry are matter of intense debate. Whereas many diagnostic entities currently used in psychiatry are characterized by good reliability, they are hampered by poor validity*».*

We would argue that, at least for some patients, ***formulation, rather than diagnosis****, should be the cornerstone in clinical practice.*

The focus is on classifying factors understanding how they impact on the patient.

Of note, formulations exist even before the patient presents to the clinician and, as such, before the diagnosis.

Formulation "serves both as a map for therapy and a guide to which map to choose."

WHEN TO CONSIDER A PHARMACOLOGICAL APPROACH?

- Antipsychotic medications are not usually indicated;

- **Exceptions should be considered when:**

- rapid functional deterioration is occurring,
- severe suicidal risk is present and treatment of any depression has proved ineffective;
- Increased aggressive behaviors.

International Guidelines 2005

- If antipsychotics are considered, ideally **Atypical AP** should be used in **low doses** and for a **limited period**.

- If there is benefit and resolution of symptoms **after 6 weeks**, the medication may be continued with the patient's consent for a further ***6 months to 2 years***;

- After this period, a gradual attempt to withdraw the medication should be made if there has been a good recovery.

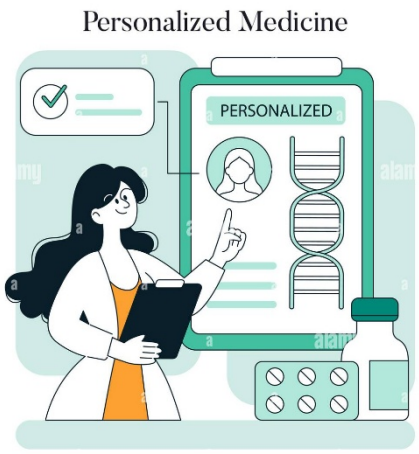
International Guidelines 2005

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 21 May 2019
doi: 10.3389/fpsyt.2019.00345

Individualized Prediction of Transition to Psychosis in 1,676 Individuals at Clinical High Risk: Development and Validation of a Multivariable Prediction Model Based on Individual Patient Data Meta-Analysis

Aaltsje Malda[1,2], Nynke Boonstra[1,3], Hans Barf[3], Steven de Jong[4], Andre Aleman[2,5], Jean Addington[6], Marita Pruessner[7,8], Dorien Nieman[9], Lieuwe de Haan[9], Anthony Morrison[10,11], Anita Riecher-Rössler[12], Erich Studerus[12], Stephan Ruhrmann[13], Frauke Schultze-Lutter[14], Suk Kyoon An[15], Shinsuke Koike[16,17,18,19], Kiyoto Kasai[16,17,18,19], Barnaby Nelson[20,21], Patrick McGorry[20,21], Stephen Wood[20,21,22], Ashleigh Lin[23], Alison Y. Yung[20,21,24,25], Magdalena Kotlicka-Antczak[26], Marco Armando[27,28], Stefano Vicari[29], Masahiro Katsura[29], Kazunori Matsumoto[29,30,31], Sarah Durston[32], Tim Ziermans[9,33], Lex Wunderink[1,34], Helga Ising[35], Mark van der Gaag[35,36], Paolo Fusar-Poli[37,38,39,40†] and Gerdina Hendrika Maria Pijnenborg[2,41†]*

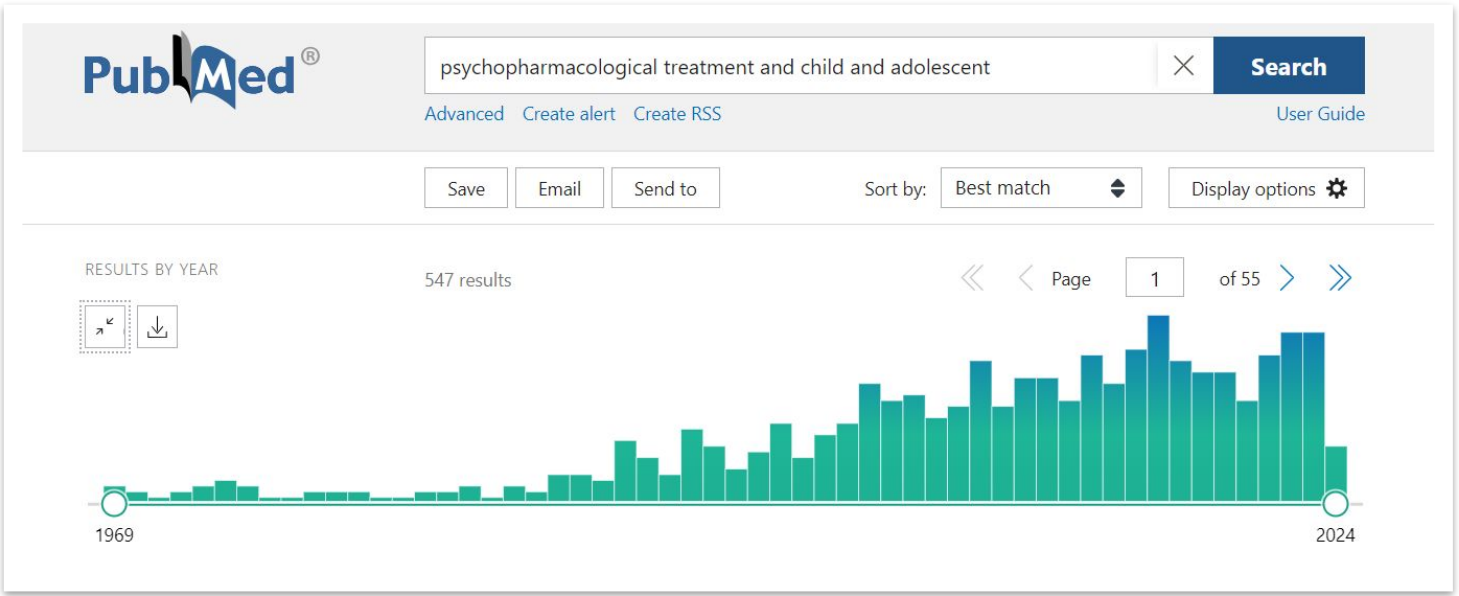


- An **individualized prognostic model based on clinical predictors** available in clinical routine was developed and internally validated, reaching only moderate prognostic performance.

- Although personalized risk prediction is of great value in the clinical practice, **because of the current high diagnostic, prognostic, and therapeutic heterogeneity of CHR-P, future developments are essential,** including the refinement of the prognostic model and its external validation.

Over the past few decades, relatively stable evidences have been generated from randomized controlled trials and observational studies assessing the efficacy, effectiveness, tolerability, and safety of medications for specific disorders in child and adolescent mental health.

Paucity of new compounds



NUTRACEUTICS

Meta-Analysis > World J Biol Psychiatry. 2022 Jul;23(6):424-455

Early Intervention IN PSYCHIATRY

ORIGINAL ARTICLE

Omega-3 fatty acids and neurocognitive ability in young people at ultra-high risk for psychosis

Alison McLaverty, Kelly A. Allott, Maximus Berger, Rob Hester, Patrick D. McGorry, Barnaby Ne
Connie Markulev, Hok Pan Yuen, Miriam R. Schäfer, Nilufar Mossaheb, Monika Schlögelhofer,
Stefan Smesny, Ian B. Hickie, Gregor Emanuel Berger, Eric Y. H. Chen, Lieuwe de Haan, Dorien
Merete Nordentoft, Anita Riecher-Rössler, Swapna Verma, Andrew Thompson, Alison Ruth Yu
G. Paul Amminger ... See fewer authors

First published: 06 September 2020 | https://doi.org/10.1111/eip.13025 | Citations: 8

Review > Early Interv Psychiatry. 2022 Jan;16(1):3-16. doi: 10.1111/eip.13133. Epub 2021 Mar 2.

Omega-3 fatty acid in ultra-high-risk psychosis: A systematic review based on functional outcome

R Cotter [1]

Multicenter Study > Biol Psychiatry. 2020 Feb 1;87(3):243-252.

doi: 10.1016/j.biopsych.2019.08.030. Epub 2019 Sep 18.

The NEURAPRO Biomarker Analysis: Long-Chain Omega-3 Fatty Acids Improve 6-Month and 12-Month Outcomes in Youths at Ultra-High Risk for Psychosis

G Paul Amminger [1], Barnaby Nelson [2], Connie Markulev [2], Hok Pan Yuen [2], Miriam R Schäfer [2], Maximus Berger [2], Nilufar Mossaheb [3], Monika Schlögelhofer [3], Stephan Smesny [4], Ian B Hickie [5], Gregor E Berger [6], Eric Y H Chen [7], Lieuwe de Haan [8], Dorien H Nieman [8], Merete Nordentoft [9], Anita Riecher-Rössler [10], Swapna Verma [11], Andrew Thompson [2], Alison Ruth Yung [12], Patrick D McGorry [2]

Evidence suggests a role of **omega-3 fatty acids** for prevention of transition to psychosis in high-risk youth, with potential pre-existing fatty acid deficiency.

frontiers | Frontiers in Psychiatry

TYPE Systematic Review
PUBLISHED 18 July 2023
DOI 10.3389/fpsyt.2023.1231710

Questioning the role of palmitoylethanolamide in psychosis: a systematic review of clinical and preclinical evidence

Riccardo Bortoletto[1]*, Fabiana Piscitelli[2], Anna Candolo[1], Sagnik Bhattacharyya[3], Matteo Balestrieri[1] and Marco Colizzi[1,3]*

Included: 13 studies (11 human, 2 animal)

BACKGROUND

- The **endocannabinoid (eCB) system** disruption has been suggested to underpin the development of psychosis, fueling the search for novel, bettertolerated antipsychotic agents that target the eCB system.

- Among these, **palmitoylethanolamide (PEA)**, an N-acylethanolamine (AE) with neuroprotective, anti-inflammatory, and analgesic properties, has drawn attention for its antipsychotic potential

- Observational studies **investigating PEA tone in psychosis patients** converged on the evidence for increased PEA plasma (6 human) and central nervous system (CNS; 1 human) levels, as a potential early compensatory response to illness and its severity, that seems to be lost in the longer-term (CNS; 1 human), opening to the possibility of **exogenously supplementing it to sustain control of the disorder** .

- **Consistently, PEA oral supplementation reduced negative psychotic and manic symptoms among psychosis patients**, with no serious adverse events (3 human).

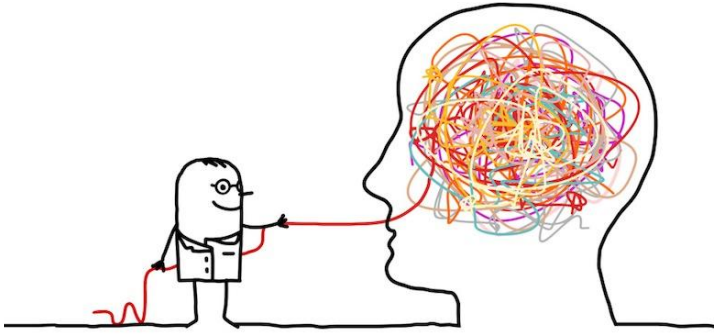
WHAT ABOUT PSYCHOLOGICAL-PSY CHOEDUCATIVE INTERVENTIONS?

The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 62:5 (2021), pp 657–673 doi:10.1111/jcpp.13322

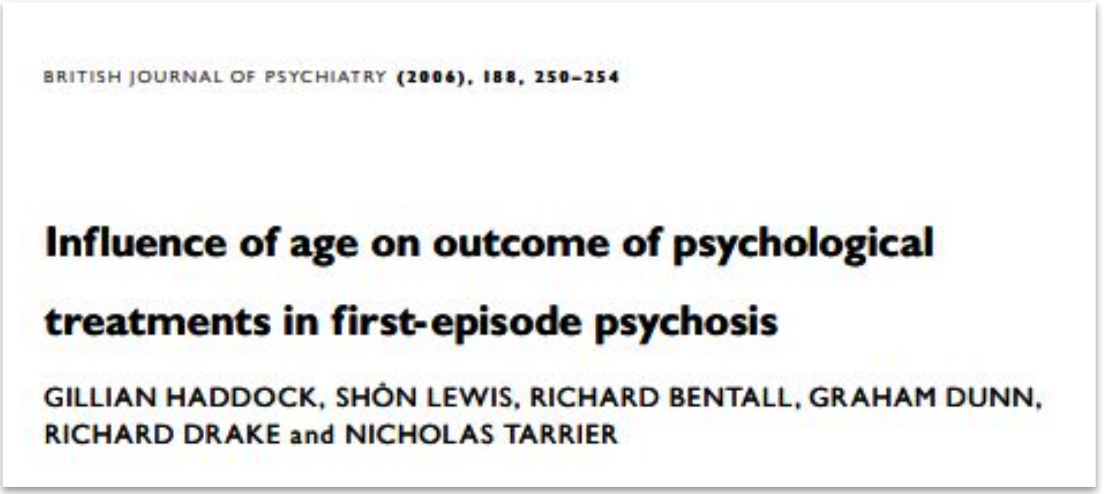
Annual Research Review: Prevention of psychosis in adolescents – systematic review and meta-analysis of advances in detection, prognosis and intervention

Ana Catalan,[1,2,†] Gonzalo Salazar de Pablo,[2,3,†] Julio Vaquerizo Serrano,[2,3] Pierluca Mosillo,[2,4] Helen Baldwin,[2] Aranzazu Fernández-Rivas,[1] Carmen Moreno,[3] Celso Arango,[3] Christoph U. Correll,[5,6,7,8] Ilaria Bonoldi,[2,‡] and Paolo Fusar-Poli[2,9,10,11,‡]



- There was **not enough evidence to recommend one specific treatment** (including CBT) over the others (including control conditions);
- RCTs suggested that **family interventions** and **cognitive remediation** improve **cognition, symptoms and functioning** but not the illness progression.

EOS/VEOS: CBT



BRITISH JOURNAL OF PSYCHIATRY (2006), 188, 250–254

Influence of age on outcome of psychological treatments in first-episode psychosis

GILLIAN HADDOCK, SHÔN LEWIS, RICHARD BENTALL, GRAHAM DUNN, RICHARD DRAKE and NICHOLAS TARRIER

- RCT designed to evaluate the effectiveness of **CBT** *vs* **supportive counselling** *vs* **treatment as usual** (sample: n = 304, young adults):

- **3-month follow-up**: In the EOS group, supportive counselling was more effective than CBT.
- **18-month follow-up**: Among EOS participants who adhered to CBT, an increase in insight was observed.

Review > Transl Psychiatry. 2021 Jan 13;11(1):43. doi: 10.1038/s41398-020-01165-x.

Establishing a clinical service to prevent psychosis: What, how and when? Systematic review

Gonzalo Salazar de Pablo [# 1 2], Andrés Estradé [# 1 3], Marcello Cutroni [4], Olivier Andlauer [5 6], Paolo Fusar-Poli [7 8 9 10]

The first rate-limiting step to successfully translate prevention of psychosis in to clinical practice is to establish specialised Clinical High Risk for Psychosis (CHR-P) services.

Fifty-six studies (1998-2020) were included, encompassing **51 distinct CHR-P services** across **15 countries** and a catchment area of **17,252,666** people.

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European Neuropsychopharmacology 93 (2025) 58–65

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Lack of transparency on baseline pharmacological treatments in Clinical High-Risk for psychosis (CHR-P) may degrade precision: A systematic review and meta-analysis

Andrea Raballo [a,b,*], Michele Poletti [c], Antonio Preti [d]

A systematic review and meta-analysis were conducted by searching studies which included CHR-P samples, reported numeric data on outcomes at follow-up, and examined the transition to psychosis as an outcome, **focusing on baseline pharmacological exposure to antipsychotics, antidepressants, benzodiazepines, and mood stabilizers**. A total of 95 studies were analyzed.

- Overall, a non negligible fraction of CHR-P participants is already under psychoactive pharmacological treatment at enrollment.

Table 1
Reporting pattern on baseline pharmacological exposure in 95 studies on CHR-P individuals included in the systematic review and meta-analysis.

	% of studies reporting baseline exposure	Range of baseline exposure	Meta-analytical prevalence of exposure*	% of studies reporting baseline exposure in relation to transition outcome (yes/no)
Antipsychotics	57.8 %	0.1 % – 85.2 %	24.5 % (23.4 % – 25.6 %)	31.6 %
Antidepressants	36.8 %	2.9 % - 67.7 %	30.6 % (29.1 % – 32.0 %)	18.9 %
Benzodiazepines	16.8 %	1.5 % - 48.8 %	14.6 % (12.9 % – 16.5 %)	7.4 %
Mood Stabilizers	14.7 %	0.8 % - 30.8 %	5.9 % (5.0 % – 7.0 %)	7.4 %

* Common (fixed-effects) model: point estimates and 95 % confidence interval.